MULTICOMPONENT REACTIONS IN ORGANIC SYNTHESIS: AN APPROACH TO VIRIDIN AND VIRIDIN ANALOGS

By

CLAUDE V. ROBOTHAM

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2003

This is dedicated to my mother, father and brother…my lifeline and inspiration.

ACKNOWLEDGMENTS

I would like to thank those who have made the past five years both fun and exciting. To my labmates, Buck Batson, Chris Baker, Lynn, Maria, Chris Whitehead, Jeff, and Ravi, I could only hope to work again with such interesting people. I think we have forever changed the meaning of "lab work." and I wish all of you the best. I would also like to thank other group members whom I had the opportunity to work with, Aschwin, Todd Huml, Lee Walker, and everyone else I have encountered at the University of Florida.

I would like to thank Dr. Wright for his patience, guidance and understanding. He allowed me to take my own path toward reaching my goals and I appreciate his confidence in me. He has opened my eyes to the world of chemistry and I am happy to have been part of his group. I thank him for everything.

I would like to thank Dr. Battiste, Dr. Hudlicky, Dr. Palenik and Dr. Sloan for participating on my thesis committee. I would especially like to thank Dr. Battiste for his helpful discussions, but more importantly, as someone with a positive attitude and outlook in pure science.

To the rest of the chemistry faculty and especially those in the chemistry business office, I would like to thank all of them for their help and the opportunity to continue my studies.

Lastly and most importantly, I would like to dedicate this thesis to my family. Their love and support has made this and everything else possible. I love all of them very much. Thank you.

TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS iii

ABSTRACT vii

CHAPTER

1 MULTICOMPONENT REACTIONS IN CHEMISTRY 1

Ugi and Passerini Reactions 2
Multicomponent Reactions in Natural Product Synthesis 3
Other Examples of MCR Processes 4
Multi-component Processes in Combinatorial Libraries 7
Expanding The Scope of Ugi And Passerini MCR's 11
Tandem Ugi / Diels-Alder Reaction Toward the Synthesis of Viridin 15

2 MULTI-COMPONENT REACTIONS TOWARD THE SYNTHESIS OF VIRIDIN AND VIRIDIN ANALOGS 17

Mechanistic Studies 20
Synthetic Attempts and Approaches 22
Research Design 25
Results and Discussion 26
Conclusions 31
Experimental Section 33
UGI Procedures and Results 34
Passerini Procedure 48

3 A MULTICOMPONENT REACTION APPROACH TO THE SYNTHESIS OF HIGHLY DIVERSE POLYMERS WITH POLYPEPTIDE-LIKE FEATURES 56

Results and Discussion 56
Conclusion 65
General Reagents for the Synthesis of Monomers and Polymers 65
General Procedure for Preparation of Monomers [93a-d], [97a, 97b] 66
Chemical Characteristics of Representative Compounds 67
General Procedure for the Synthesis of ROMP Polymers [95a-d], [99a-c] 74

4 A COUPLING AND CLAISEN REARANGEMENT APPROACH TO THE SYNTHESIS OF VIRIDIN 75

Suzuki Coupling Approach 75
Claisen Rearrangement Approach to Viridin Analog 80
Conclusion 82
Experimental Section 83

APPENDIX NMR (^{1}H & ^{13}C) SPECTRA OF SELECTED COMPOUNDS 93

LIST OF REFERENCES 139

BIOGRAPHICAL SKETCH 144

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

MULTICOMPONENT REACTIONS IN ORGANIC SYNTHESIS:
AN APPROACH TO VIRIDIN AND VIRIDIN ANALOGS

By

Claude V. Robotham

August 2003

Chair: Dennis L. Wright
Major Department: Chemistry

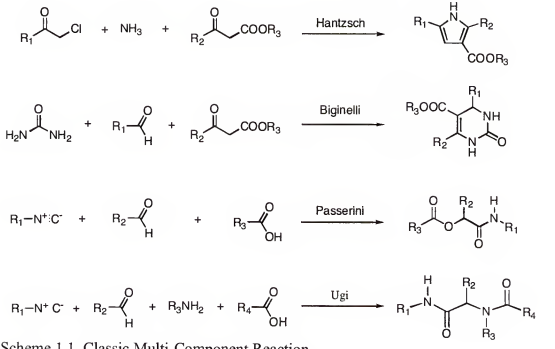
The use of the Passerini (3CC) and Ugi (4CC) reactions to construct novel analogs of the viridin family of furanosteroids and the synthesis of monomers for use in ring opening metathesis polymerization (ROMP) reactions was examined.

A strategy for the synthesis of viridin and wortmannin analogs was investigated that would maintain a high degree of synthetic flexibility while allowing for quick and efficient synthesis of a large number of analogs. The synthesis of highly functionalized oxabicyclo[2.2.1]heptadiene derivatives through the sequential use of an Ugi or Passerini multi-component coupling reaction was examined. The multicomponent reaction allowed for the quick assembly of a large number of structurally diverse products that were subjected to an intramolecular acetylene/furan Diels-Alder reaction. This tandem reaction provided derivatives that can be further functionalized to give analogs of potent PI-3K inhibitors viridin and wortmannin.

The combined application of multicomponent coupling reactions and olefin metathesis chemistry for the preparation of new chemical entities with application as novel biomaterials was also investigated. The compatibility of these two complexity-building reactions made them ideal for the use in generation of novel monomer and polymeric structures. The peptide-like functionality of the resulting monomers may allow for metal binding with application as metal scavenging agents or macromolecular ligands for asymmetric synthesis.

CHAPTER 1
MULTICOMPONENT REACTIONS IN CHEMISTRY

The search for library generating synthetic methodologies, which demonstrate chemical efficiency, diversity and complexity, has become a major focus over the past decade.[1] One class of reactions that has found widespread use in the generation of complex-molecule libraries is multi-component reactions (MCR). A true multi-component reaction involves the one-pot condensation of three or more reactants to yield a product with functionality incorporated from all of the different components. Many of these reactions work effectively in solution or mounted on solid support. Multi-component reactions begin to approach the level of an "ideal" synthesis as described by Wender et al.[2] In a single chemical transformation, MCR's utilize simple, commercially



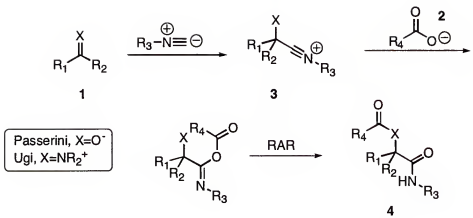
Scheme 1.1. Classic Multi-Component Reaction

available starting materials to generate products of increased complexity. The process is very efficient because almost all of the molecular weight of the individual components is retained in the final product (high atom economy as defined by Trost[3]).

Ugi and Passerini Reactions

Many of these reactions are characterized by a high concentration of heteroatoms in the product and have largely been employed for the synthesis of various heterocycles (Scheme 1.1). Many of these MCR reactions are quite old, but have found new applications in the quest for the synthesis of complex libraries. Two of the earliest reports of MCR processes were the Hantzsch pyrrole and Biginelli pyrimidine synthesis. On the other hand, the MCR's that have proved the most useful in the construction of combinatorial libraries are the Passerini and Ugi reactions.

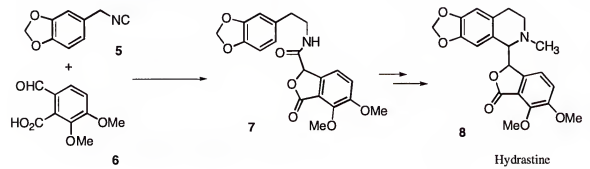
The Passerini reaction is a three-component reaction incorporating an aldehyde (or ketone), carboxylic acid and an isocyanide in a one-pot reaction to yield an α–acyloxycarboxamide. In the case of the Ugi reaction, four components are utilized; an aldehyde, amine, carboxylic acid and an isocyanide are mixed together in one-pot to yield the condensed α-amidocarboxamides. The mechanisms of these reactions (Scheme 1.2) are considered to involve an initial attack of the isocyanide on an aldehyde (Passerini) or iminium ion (Ugi) **1** followed by attack of a carboxylate **2** on the resultant nitrilium ion **3.** A final acyl migration ensues to deliver the product **4**. Since the products of the Ugi reaction represent a dipeptide-like structure, this reaction has found widespread use in the synthesis of peptidic libraries. MCR's are generally useful for preparing dipeptide-like core structures quickly and efficiently.



Scheme 1.2: Proposed Passerini and Ugi Mechanism

Multicomponent Reactions in Natural Product Synthesis

The power of these reactions has found some use in natural product synthesis. The Ugi reaction has been used in the synthesis of amino acids, polysaccharide and peptide derivatives.[4] A nice example of the Passerini reaction in alkaloid chemistry is the short synthesis of (±)-hydrastin by Falck and Manna.[5]

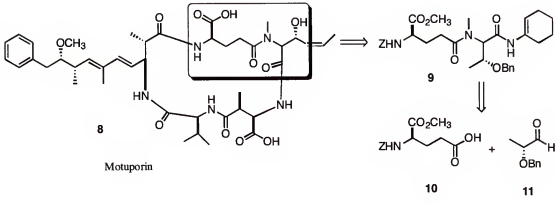


Scheme 1.3: MCR in the synthesis of hydrastine

This elegant example of the power of MCR reaction employs an interesting modification whereby the aldehyde and acid functionality are present on the same component which gives rise to a cyclic product (Scheme 1.3). Condensation of the benzylic isocyanide **5** and the carboxy aldehyde derivative **6** resulted in Passereini

reaction to generate the lactone intermediate **7**. A final Bischler-Napieralski cyclization generated the isoquinoline ring of the natural product.

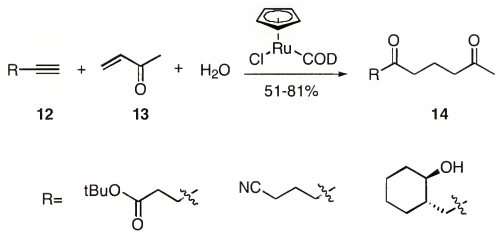
Armstrong and Bauer utilized the Ugi reaction to synthesize the 2-(N)-methylaminobutenyl fragment in their total synthesis of motuporin **8**.[6] This key fragment, **9**, was envisioned to arise through an Ugi MCR. Condensation of the chiral building blocks **10** and **11** along with methylamine and cyclohexyl isocyanide gave the amide intermediate in good yield (Scheme 1.4).



Scheme 1.4: Ugi synthesis of a motuporin fragment

Other Examples Of MCR Processes

The power associated with multi-component reactions, whereby several low-complexity materials are converted in a single step to a high-complexity product, has triggered the search for other efficient MCR's. Trost and Pinkerton[7] have developed a three-component Ru-catalyzed reaction to form substituted 1,5-diketones from alkynes, enones and water.

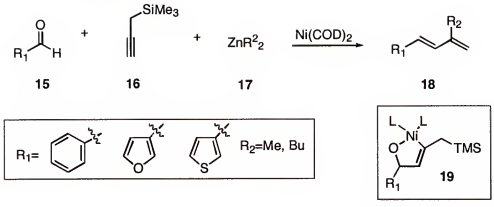


Scheme 1.5: MCR synthesis of 1,5-diketones

This process is proposed to occur by an initial ruthenium catalyzed addition of water to the acetylene **12** to give an intermediate ruthenium enolate (Scheme 1.5). The enolate is then proposed to undergo a conjugate addition with the enone **13** to give the dicarbonyl product **14** after protonation. The reaction gives the products in good yields and tolerates several functional groups (nitrile, ester, alcohol) although a primary carboxamide did give reduced yields.

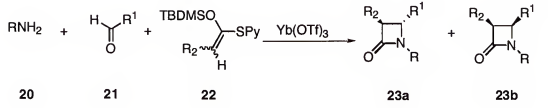
Another example that shows the power of transition metals for the synthesis of diverse compounds is a report by Montgomery and Qi who employed a low-valent nickel catalyst in a three-component synthesis of highly valued 1,3-dienes (Scheme 1.6).[8]

This three-component coupling reaction involves an aldehyde, propargyl silane and an organozinc to prepare substituted 1,3-dienes. The authors suggest that the mechanism involves an initial coupling of the acetylene **16** and the aldehyde **15** to give an intermediate oxametallacycle **19**. Transmetalation of the organozinc **17** to the nickel is followed by reductive coupling to place the R_2 substituent on the alkene. Silica gel promoted elimination of the hydroxyl and trimethylsilyl groups leads to the diene **18**.



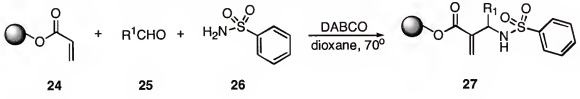
Scheme 1.6: MCR synthesis of 1,3-dienes

The Cozzi research group have described a nice three component coupling mediated by a lanthanide catalyst to produce β-lactams from silylketene thioacetals (Scheme 71.).[9]



Scheme 1.7: MCR synthesis of β-lactams

Condensation of an amine **20** and aldehyde **21** diversity element gives an intermediate imine that undergoes a [2+2] cycloaddition with the thioketeneacetal **22** to directly form differentially substituted β-lactams **23a** and **23b** as isomeric mixtures.



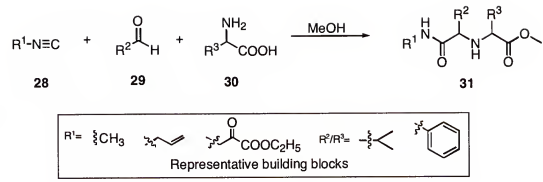
Scheme 1.8: MCR synthesis of sulfonamides.

Under Baylis-Hillman conditions, substituted sulfonamides were recently synthesized by Richter and Jung [10] *via* a resin bound three-component reaction (Scheme 1.8). This solid-phase application provides an excellent scaffold for combinatorial libraries. Dabco promoted condensation between a resin bound acrylate **24** and various aldehydes **25** in the presence of a sulfonamide **26** gave the MCR products **27** in good yield.

Multi-component Processes In Combinatorial Libraries

The high level of complexity increase in these reactions has caused MCR's to gain importance in terms of potential application to combinatorial chemistry.[11] New types of MCR's are constantly appearing in the literature,[12] and will be certain to increase the role of these reactions in the production of molecular diversity. Although many of these reactions should find wide use in library synthesis, the Passerini/Ugi reaction currently stands out as the key MCR for library synthesis.

As early as 1961, Ugi and Steinbrücker recognized that the Ugi reaction had the potential to produce large numbers of structurally diverse compounds.[13] They chose three isocyanides **28**, three aldehydes **29** and three amino acids **30** in order to generate a mixture which theoretically contained 27 compounds (54 compounds including stereoisomers) in one step **31** (Scheme 1.9).[14]



Scheme 1.9: Synthesis of a library by MCR

Armstrong and co-workers used a similar protocol on solid-support to create a 96-member library featuring an α-acylamino core. Weber and co-workers demonstrated that extremely large collections of compounds would be available from an Ugi four-component coupling.[15] They were using a genetic algorithm to examine the biological activity of a library. They chose 10 isocyanides, 40 aldehydes, 10 amines, and 40 carboxylic acids in order to generate a library of 160,000 possible products.[16]

Armstrong and co-workers utilized the Passerini reaction to assemble the core structure for analogs of azinomycin, a potent antitumor antibiotic (Figure 1).[17] It was

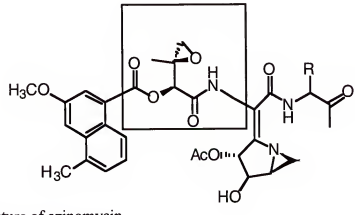
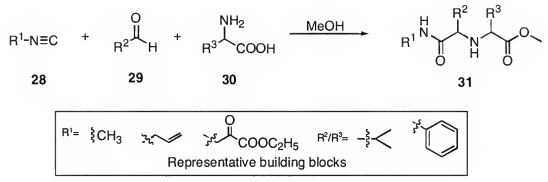


Figure 1. Structure of azinomycin



Scheme 1.9: Synthesis of a library by MCR

Armstrong and co-workers used a similar protocol on solid-support to create a 96-member library featuring an α-acylamino core. Weber and co-workers demonstrated that extremely large collections of compounds would be available from an Ugi four-component coupling.[15] They were using a genetic algorithm to examine the biological activity of a library. They chose 10 isocyanides, 40 aldehydes, 10 amines, and 40 carboxylic acids in order to generate a library of 160,000 possible products.[16]

Armstrong and co-workers utilized the Passerini reaction to assemble the core structure for analogs of azinomycin, a potent antitumor antibiotic (Figure 1).[17] It was

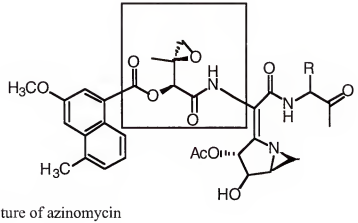
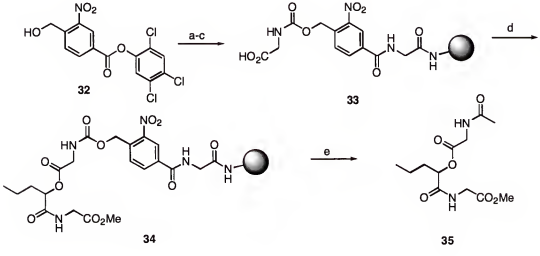


Figure 1. Structure of azinomycin

recognized that several key structural features of azinomycin, such as the epoxide, naphthoate and aziridine, were positioned on a central acyloxyamido scaffold.[18]

These workers examined the use of an Ugi MCR to assemble various analogs containing these different moieties. Because the core structure is sensitive to both acidic and basic reagents, a synthetic strategy was developed to accommodate the sensitive functionality of azinomycin analogs (Scheme 1.10).[19] In order to accommodate the labile functionality found in these compounds, Armstrong opted for the use of a linker that would release the compounds under mild photochemical conditions. Installation of a carbamate linker on the benzylic alcohol **32** was followed by acylation of an MBHA resin with the activated ester. Conversion of the ester to the carboxylic acid set the stage for



Scheme 1.10: Approach to azinomycin analogs. Key: (a) EtO_2CCH_2NCO; (b) MBHA-Gly-Resin, HOBt; (c) LiOH (d) MeO_2CCH_2NC, $OHCCH_2CH_2CH_3$; (e) 365 nm, Ac_2O, MeCN.

a Passerini reaction (**33-34**) ,which was initiated by the addition of simple aldehyde and isonitrile building blocks. The resultant acyloxyamides **34** were removed from the resin by photolysis (365 nm) in the presence of acetic anhydride to give the final products as the corresponding acetamides **35**. Utilizing this methodology, Armstrong was able to

prepare several simplified azinomycin analogs with various levels of biological activities (Figure 2).

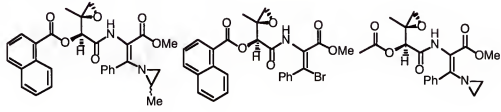
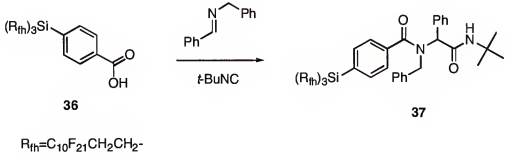


Figure 2. Representative azinomycin analogs from Passerini reaction

Studer et al. have developed a fluorous protocol for the Ugi and Biginelli reaction in order to take advantage of the ease of purification of fluorous compounds (Scheme 1.11).[20] A fluorous silane substituted acid **36** is used as a fluorous equivalent of a resin and a means to separate the library components from either organic or aqueous solvents *via* liquid-liquid extraction with fluorous solvents. Once the library **37** is prepared, the fluorous handle can be easily removed through desilylation with TBAF.



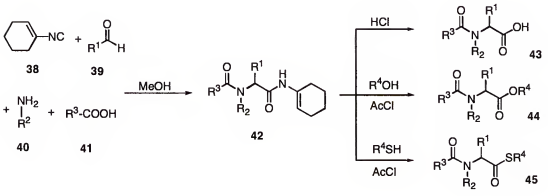
R_{fh}=$C_{10}F_{21}CH_2CH_2$-

Scheme 1.11: Synthesis of a fluorous phase library

Expanding The Scope Of Ugi And Passerini MCR's

The power of these multi-component reactions has inspired others to develop methods that expand the level of complexity possible with these types of MCR's. In the case of the Ugi reaction, one of the primary limitations is the number of commercially

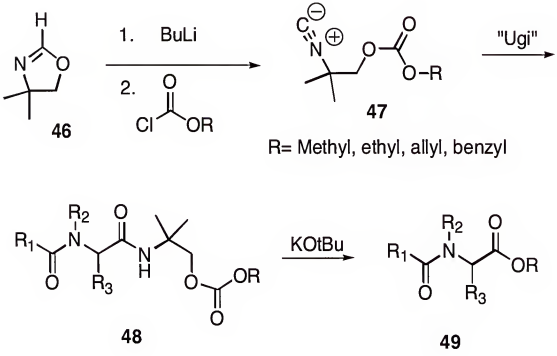
available isocyanides.[21] The somewhat difficult preparations for functionalized isocyanides means that there are less of these key building blocks available than the corresponding acids, amines and aldehydes. Armstrong and Keating[22] were able to expand the Ugi reaction by developing a "convertible isocyanide." This type of isocyanide is defined as one that can undergo further, diversity building sequences after the MCR reaction is complete.



Scheme 1.12. Convertible isocyanide

Ugi's 1-isocyanocyclohexene **38**, synthesized in the early 60s, [23] can be used in the Ugi reaction and subsequently converted under mild acid conditions to a variety of other functionalities. Ugi reaction with components **38**-**41** generates the library products **42**. The labile enamide generated from component **38** allows the library to be further diversified by conversion to the corresponding carboxylic acids **43**, esters **44** or thioesters **45** (Scheme 1.12).[24] This conversion allows for increased diversity of Ugi and Passerini type libraries and helps to overcome some of the restrictions due to the limited number of available isocyanides. Recently, Ugi and co-workers have made another contribution to the use of convertible isocyanides for MCR processes through the development of (β-

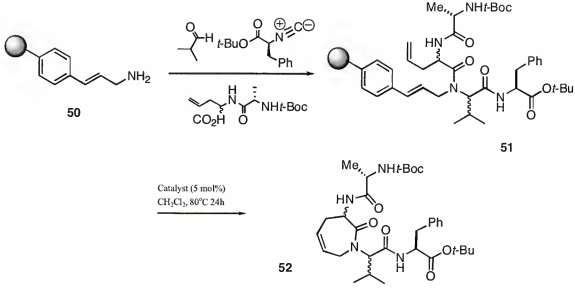
isocyano-ethyl)-alkyl-carbonates (Scheme 1.13) that can be converted to *N*-acylated α-amino acids and esters under mildly basic conditions.[25]



Scheme 1.13: Diversity with convertible isocyanides

Lithiation of the oxazoline derivative **46** induces fragmentation of the heterocycle to give an alkoxy substituted isonitrile **47** that can be acylated with a variety of chloroformates to give the carbonate derivatives **48**. Ugi-4CC reaction gives the standard Ugi products that can be rearranged under basic conditions to give the ester derivatives **49**. The reaction is proposed to involve an initial cyclization of the amide and carbonate to form an acyl oxazolidinone derivative that is deacylated by the alkoxide (generated form the original carbonate) to give the ester. The overall process transfers the available diversity of chloroformates to the position normally generated from the isonitrile.

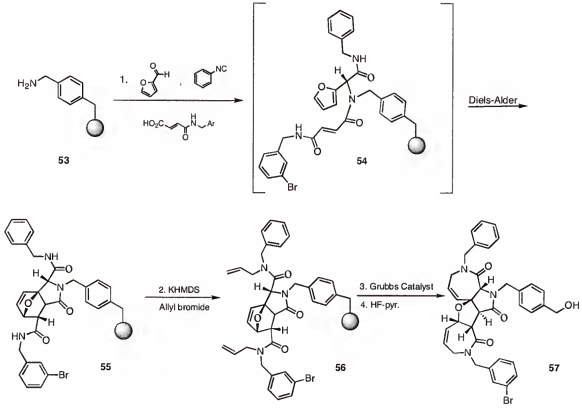
While the convertible isocyanide increases the ability of the Ugi and Passerini reactions to produce more diverse products, there is still the issue of chemical complexity. Tandem reactions, in which a one-step reaction yields the starting material for the next one-step chemical transformation, can efficiently increase molecular complexity. Pisocopio and co-workers were able to utilize the 4-component Ugi reaction in conjunction with a ring-closing metathesis in order to prepare several β-turn mimics of the Freidlinger lactam class of peptide mimetics (Scheme 1.14).[26]



Scheme 1.14: Tandem Ugi/RCM process

The strategy used in this approach involved an initial Ugi reaction in which the amine component **50** was a resin bound allylic amine. Upon completion of the reaction, the Ugi products **51** were removed from the resin. Treatment of the supported compounds with the Grubbs ruthenium alkylidene complex simultaneously cleaves the allyl amine from the resin and promotes an intramolecular ring-closing metathesis to form the key caprolactam subunit of the turn mimic **52**. Intramolecular Diels-Alder

cycloadditions have emerged as an effective method to generate more complex polycyclic systems from MCR products. Paulvannan[27] successfully executed a one-pot tandem 4-component Ugi coupling and intramolecular Diels-Alder reaction. This process was recently expanded by Schreiber and co-workers[28] to include a ring-opening/ring closing metathesis process as a subsequent reaction to build highly complex products in short, efficient sequences.



Scheme 1.15: Tandem reactions for diversity generation

A resin bound amine **53** was employed as a component in an Ugi condensation with a substituted acrylic acid, benzylisocyanide and furfuraldehyde. The initial Ugi adduct **54** was poised for an intramolecular Diels-Alder reaction with the pendant furan which occurred spontaneously to generate the oxo-bridged cycloadduct **55** (Scheme 1.15). The resulting amides were allylated under standard conditions to give **56** as a

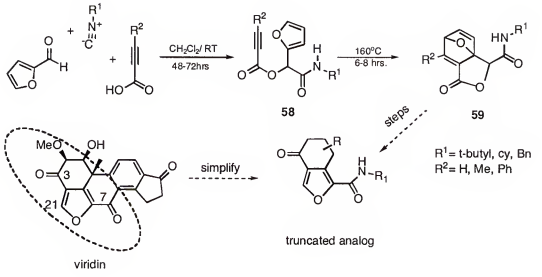
prelude to a key ruthenium promoted bond reorganization. Exposure of the Diels-Alder adduct to a modified Grubbs catalyst affected a strain-driven opening of the oxa-bicyclo[2.2.1]heptene ring which was followed by two ring-closing reactions to generate two seven-membered heterocycles **57**. The use of three consecutive complexity-increasing reactions (Ugi, IMDAF and olefin metathesis) illustrate the potential for generating complex libraries where the diversity and complexity of the library begins to resemble the complex molecules of nature rather than those generated synthetically.

Our laboratories are currently examining the use of a tandem Passerini MCR and an intramolecular furan Diels-Alder reaction to prepare truncated analogs of the phosphatidyl inositol-3-kinase inhibitor viridin and other furanosteroids.[29] These compounds are proposed to inhibit the function of the enzyme by alkylation of a key active site residue (Lys 802).[30] This alkylation involves attack of the lysine amino sidechain on to the C21 position of the furan which is electrophilic by virtue of the C3 and C7 electron-withdrawing groups. Ring opening of the furan then occurs possibly promoted by ring strain in the annulated furan.

Tandem Ugi / Diels-Alder Reaction Toward The Synthesis of Viridin

We are pursuing the synthesis of a library of compounds representing the minimum active core to establish synthetically simpler compounds that can inhibit the enzyme. The designed truncated molecule still retains the key features such as the two electron-withdrawing groups and some strain through the fusion of the furan to the six-membered ring. We have examined the potential of a tandem Passerini condensation/Diels-Alder reaction to build these basic core structures that may retain biological activity. Three-component coupling of isocyanides and -ynoic acids with 2-furfural provided the Passerini products **58** after extended reaction times. Subsequent thermal Diels-Alder

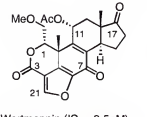
reactions delivered the oxo-bridged products **59** in good yield. These compounds are under study for their conversion to the truncated analogs.



Scheme 1.16: Tandem reactions toward viridin analogs

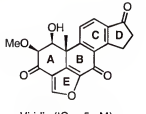
CHAPTER 2
MULTI-COMPONENT REACTIONS TOWARD THE SYNTHESIS OF VIRIDIN AND VIRIDIN ANALOGS

The design, synthesis and evaluation of small molecule inhibitors of phosphatidyl inositiol-3-kinase (PI-3K) could ultimately lead to the development of highly specific biological probe agents or new therapeutic agents for the treatment of cancer. Wortmannin **60**, viridin **61** and demethoxyviridin **62** were first isolated in the 1950's from *Talaromyces wortmanni* and *Trichoderma viride*.[31] They are highly oxygenated furanosteroids that were recently identified as potent inhibitors (IC_{50}= 2-5nM) of the catalytic function of PI-3K.[32] These molecules behave as potent analogs of ATP **63** and have been shown to bind in a quasi-irreversible manner to the enzyme. However, as with most ATP analogs these compounds show cross-reactivity with other ATP binding enzymes. This can produce misleading results in biological studies and can hinder the development of new drugs that target oncogenic kinases.



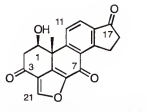
Wortmannin (IC_{50}=2-5nM)

60



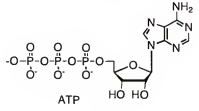
Viridin (IC_{50}=5-nM)

61



Demethoxyviridin (IC_{50}=2-nM)

62



ATP

63

The inhibition of oncogenic kinases has been shown to be an effective strategy for combating certain types of cancer. The inhibition of PI-3K could be equally important for the treatment of cancers that result from a malfunction of this signaling pathway. The viridin family of natural products presents a highly effective platform upon which to design potential inhibitors of PI-3K. Recent x-ray structural data of the inhibitors bound to the enzyme provides high-resolution information that has recently reinforced our approach.[33] Key interactions can be studied and further help fine-tune analog approaches (Figure 3). Our goal over the past four years has been to develop and synthesize new PI-3K inhibitors based on these natural products.

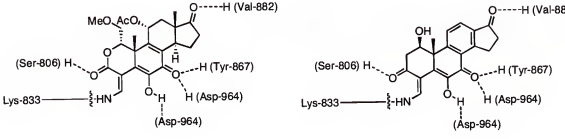
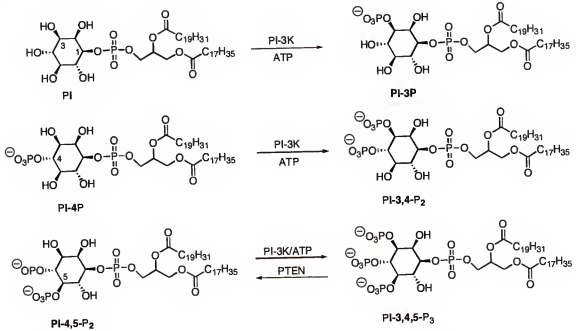


Figure 3: Key interactions of wortmannin and demethoxyviridin

The importance of the PI-3K enzyme is it functions within cell signal transduction pathways. Signal pathways within a cell can mediate cell growth, including cell proliferation. Regulation or inhibition of these signaling pathways could lead to potential new targets for therapeutic intervention in various proliferative diseases, such as cancer.[34]

PI-3K is a heterodimeric protein composed of an 85 kDa regulatory domain (p85) and a 110 kDa catalytic domain (p110) that is found in three different isoforms (α,β,γ). It appears to be a critical enzyme and is found in organisms all the way from simple yeasts to humans. The enzyme has been shown to be important for a variety of regulatory

processes. Recent studies show that PI 3-kinase is regulated by p21ras via its association with the Ras effector site in a GTP-dependent manner.[35] PI-3K transfers the terminal phosphate of ATP to the 3' (D3) position of phosphytidylinositol (PI). The phosphorylation of PI leads the to the production of secondary messengers, phosphatidylinositol-3,5-biphosphate and phosphatidylinositiol-3,4,5-triphosphate. In turn, these messengers activate protein kinase B (PKb) which plays an inportant role in protein synthesis and glycogenesis (Scheme 2.1).[36] This is important considering that the tumor supressor protein PTEN is responsible for the inactivation of PKb by dephosphorylation of phosphatidylinositiol-3,4,5-triphosphate. Therefore, regulation of PI-3K pathways via viridin and wortmannin may be a useful tool for the study of PI-3K function and therapeutic studies.



Scheme 2.1: Phosphorylation of phosphoinositides by PI-3K

Mechanistic Studies

While both viridin and wortmannin are potent inhibitor of PI-3K, they are also potent cell cytotoxic agents causing toxic effects in rats including weight loss, internal hemorrhaging, and death.[37] Additionally, it has been reported that both display cytotoxicity in several human tumor cell lines (colon and ovarian) with IC50's in the 0.3-0.9 mg/ml range.[38] Kinetic analysis by Powis and co-workers[39] indicate that both are irreversible binders that may explain the observed toxicological effects. Norman and co-workers have proposed a mechanism for the PI-3K inhibition by these steroids based on structural-activity relationship (SAR) studies.[40] They propose that addition of the PI-3K e-amino group of lysine 802 to the C21 position on the furan moiety, followed by elimination of the furan oxygen, leads to a covalent bond to PI-3K (Figure 4).

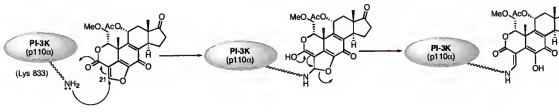
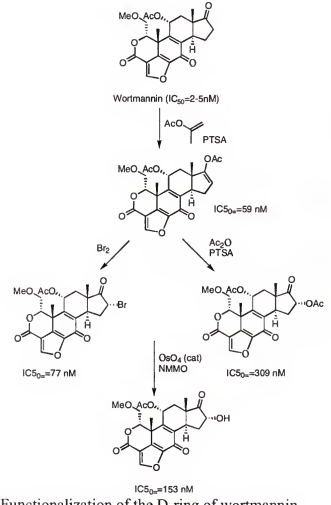


Figure 4: PI-3K addition to wortmannin

Interestingly, the furan ring of wortmannin behaves as an electrophilic rather than nucleophilic center. This is due primarily to the electron withdrawing carbonyl groups at C3 and C7. Attack on C21 by the ε-amino group of lysine 833 proceeds through a classical addition/elimination pathway to give a vinylogous carbamate. Although not rigorously established, the mechanism of inhibition by the structurally related viridins is assumed to occur through a similar manifold. The relief of ring strain in the annulated

the formation of a vinylogous carbamate/amide is another major contributor to this unusual reactivity owing to the high degree of resonance stabilization of this functionality. Evidence indicates that this reaction is best considered as a "quasi-irreversible" process since the ring opening of the furan seems to be reversible.

PI-3K inhibition assays utilizing several different nucleophiles support this mechanism and more importantly correlates to the associated toxicity observed by wortmannin-based inhibitors of PI-3K.



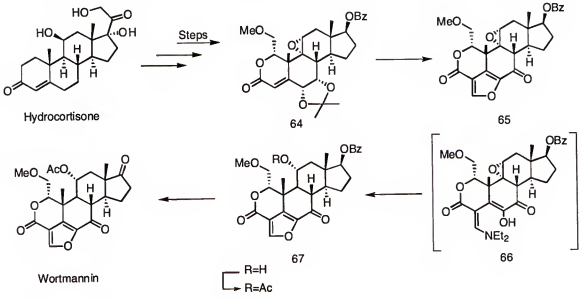
Scheme 2.2: Functionalization of the D-ring of wortmannin

Norman and co-workers also found that the D ring of wortmannin is an important recognition site since modifications have a large effect on inhibitor potency. For example, enolization of the D ring ketone shows a loss of activity by 10 fold, while analogs of this derivative show even lower activity (Scheme 2.2).[41]

While these compounds are potent inhibitors of PI-3K, they are not completly selective. Therefore, posible structural modification of these compounds may provide for a more therapeutic alternatives.

Synthetic Attempts and Approaches

While Broka and co-workers first synthesized wortmannin analogs in 1992,[42] Shibasaki and co-workers were the first to report the total synthesis of wortmannin from hydrocortisone in 1996.[43] This synthesis had several drawbacks including its length (>30 steps) and poor yields. They found that installation of the furan moiety toward the end of

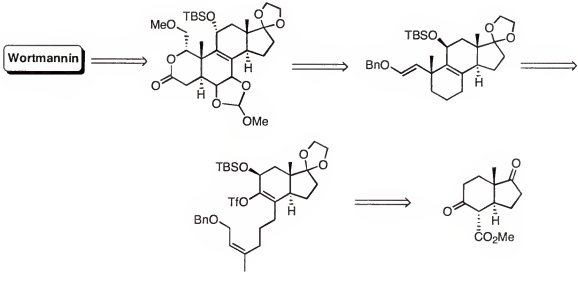


Scheme 2.3: Shibasaki synthesis of wortmannin from hydrocortisone

the synthesis proved difficult (Scheme 2.3). Treatment of **64** with

Tris(dimethylamino)methane in the presence of DBU and *N,N*-dimethylformamide dimethyl acetal at 100°C gave the aminomethylene-lactone, which was hydrolyzed with 2N HCl. The resulting alcohol was oxidized by PCC to give **65** in 11% yield. They found that conversion of **65** to **67** did not proceed unless **65** was first converted to the aminomethylene-lactone **66** by exposure to diethylamine. **66** could then be converted to **67** by treatment with DBN in CH_2Cl_2 followed by 1N HCl.

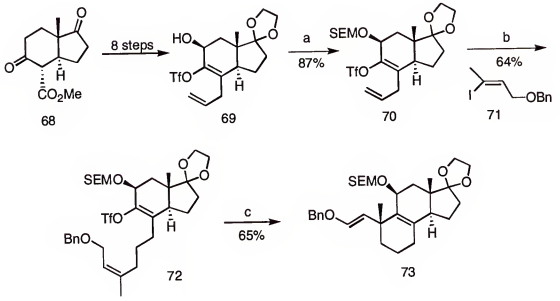
More recently, Shibasaki has developed another strategy toward the direct synthesis of wortmannin.[44] Their new synthetic strategy includes an intramolecular Heck reaction to obtain the angular methyl and formation of the B ring (Scheme 2.4). However, once again, Shibasaki plans on installing the furyl moiety toward the end of the synthesis.



Scheme 2.4: Shibasaki Heck coupling approach to wortmannin

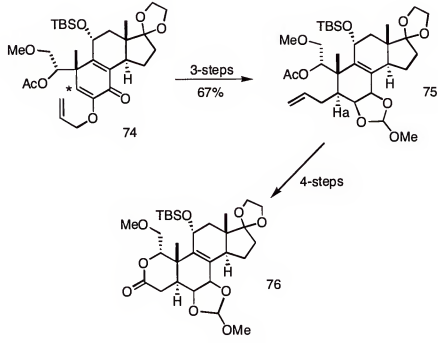
This new approach relied on two key reactions: one, an asymmetric intramolecular Heck reaction for the stereospecific construction of the allylic quaternary carbon center (Scheme 2.4) and two, a diosphenol-Claisen rearrangement to install the C-C bond at the neopentyl position* (Scheme 2.5).

The intramolecular Heck reaction on **72** to **73** proceeded smoothly in excellent yield and stereoselectivity (β-Me:α-Me = 18:1). It was observed that the β-SEM ether in **72** governs the stereoselectivity of the Heck reaction in this case. The α-SEM ether gave the undesired isomer. To date, no synthesis of Viridin has been completed.



Scheme 2.5: Intramolecular Heck reaction used by Shibasaki in wortmannin synthesis.. Key: a) SEMCl, 2,6-lutidine, nBu_4NI, CH_2Cl_2 , 40° C; b) 9-BBN, THF, RT, [$PdCl_2$(dppf)], K_3PO_4, THF/DMF, 60° C; c) 10 mol% of $Pd(OAc)_2$, 22 mol% of 1,3-bis(diphenylphosphanyl) propane, 1.0 equiv of nBu_4NBr, 2.5 mol equiv of K_2CO_3, toluene, 100° C, 17 h. SEMCl=2-(trimethylsilyl)ethoxymethyl chloride, 9-BBN= 9-borabicyclo[3.3.1]nonane, dppf= 1,1'-bis(diphenylphosphanyl)ferrocene.

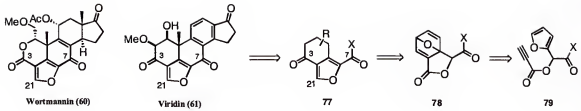
Perhaps even more elegant than the Heck coupling is the Claisen rearrangement of **74**. The task of installing a C-C bond at the sterically crowded neopentyl position was achieved by a diosphenol-Claisen rearrangement under simple thermal conditions to give the α-diketone as a single diasteromer (Scheme 2.5). After oxidation and protection to give the orthoester, **75** is converted to the lactone **76** in 4 steps.



Scheme 2.6: Diosphenol-Claisen rearrangement in wortmannin synthesis

Research Design

We have an ongoing interest in synthesizing simplified analogs of these compounds to study their biological function. The design of these simplified analogs (generalized in structure **77** is based on the hypothesis that the annulated furan in this structure contains the required features to covalently modify the enzyme. These simplified analogs retain the furan moiety, deactivated at C21 by two carbonyl groups. The E-ring is also retained to incorporate strain in the furan and provide additional sites for modification. A strategy



Scheme 2.7: Design of simplified viridin and wortmannin analogs

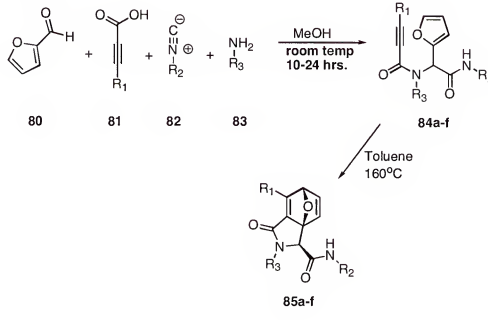
for the synthesis of these analogs was devised that would maintain a high degree of synthetic flexibility. It was envisioned that derivatives of **77** could arise from an oxabicyclo derivative **78** prepared from **79** by an intramolecular Diels-Alder reaction of furan (IMDAF) with a pendant alkyne. Placement of an amide function as the C7 carbonyl unit permits the direct and flexible preparation of **79** through a Passerini multi-component coupling reaction (MCR).[45]

Our goal for the wortmannin model study is to install the furan moiety relatively early in the synthesis. Paulvannan[46] has described an Ugi MCR reaction followed by an intramolecular Diels-Alder furan (IMDAF) reaction with an olefinic dienophile to construct combinatorial scaffolds. This was recently used by Schreiber[47] in an approach to natural product-like libraries. However, there was no information available on the use of an acetylenic dienophiles or the assembly of the cycloaddition precursors through a Passerini MCR.

Results and Discussion

We initially chose to study the sequential Ugi/IMDAF sequence using acetylenic dienophiles. Ugi condensation of 2-furaldehyde **80**, acetylenic acids **81**, isonitriles **82**

and amines **83** proved very efficient for the generation of acetylenic amides **84a-f** in high yield (Scheme 2.7).



Scheme 2.8: Synthesis of Bicyclic Lactams

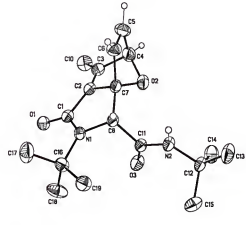
Conversion to the oxabicyclo [2.2.1] heptadiene derivatives was initially studied under Lewis acid catalysis.[48] Surprisingly, treatment with Me_2AlCl, reported to be effective for IMDAF reactions, failed to deliver any of the cycloadducts, returning either starting material or extensive decomposition products. However, it was observed that when the Ugi products were allowed to stand at room temperature, they would partially convert to the corresponding cycloadduct. A complete conversion to the adducts **85a-e** could be effected smoothly under thermal conditions in less than 24 hours. The terminal acetylene **84f** decomposed under the reaction conditions (Table 2.1).

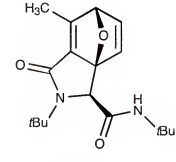
Table 2.1. Sequential Ugi/IMDAF Studies

Entry (MCR)[a]	R1	R2	R3	MCR Yield	Entry (IMDAF)[b]	IMDAF Yield[c]
84a	Me	Bn	Bn	88%	**85a**	74%
84b	Ph[d]	*t*Bu	Bn	74%	**85b**	81%
84c	Me	*t*Bu	*t*Bu	N/A[e]	**85c**	81%
84d	Me	*t*Bu	Bn	92%	**85d**	78%
84e	Ph	Bn	Bn	89%	**85e**	80%
84f	H	*t*Bu	Bn	84%	**85f**	Dec.

[a] Reactions were run at a concentration of 0.6 M in MeOH at RT. [b] A 0.02 M solution of the furan in toluene was heat at 200°C in a sealed tube. [c] Yields reported are for a pure diastereomer [d] MCRs with phenyl propynolic acid were run in the dark to limit alkyne dimerization [e] Cyclized spontaneously upon standing at RT.

The reactions were highly diastereoselective with less than 10% of any other isomers detected in the crude product. The minor isomers were easily removed upon column chromatography of the cycloadduct. The relative orientation of the carboxamide sidechain could not be assigned by NMR methods. Fortunately, an x-ray crystal structure of adduct **85c** (Figure 5) revealed that the major diastereomer possessed the *exo*-oriented sidechain. The stereochemistry of the other adducts was assigned by analogy.

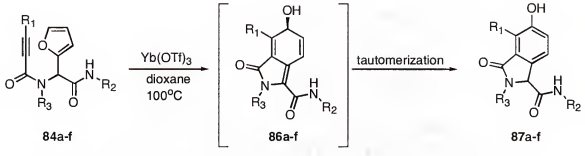




85c

Figure 5. X-ray structure of cycloadduct **85c**

While exploring the use of Lewis acids to catalyze the Diels-Alder reaction, an unprecedented cascade process was observed. Upon exposure to catalytic $Yb(Otf)_3$ in 1,4-dioxane at high temperatures, the Ugi products **84a-e** was cleanly converted to the isoindolinones **87a-e** in high yield (Scheme 2.9).



Scheme 2.9: Two-step synthesis of Isoindolinones

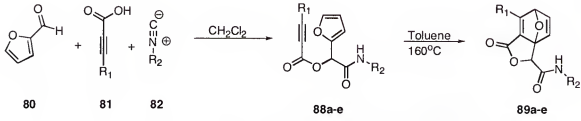
One possibility for the formation of these novel phenolic derivatives involves initial conversion to the Diels-Alder adducts **85a-e**. Lewis acid promoted opening of the oxobridge and elimination would give the unsaturated amides **86a-e**, which would be expected to tautomerize to the phenols **87a-e**. This process represents a direct synthesis of highly substituted isoindolinones in two operations from simple starting materials.

Table 2.2. Synthesis of Isoindolinones

Entry (MCR)[a]	R1	R2	R3	Entry (Phenol)[a]	Yield
84a	Me	Bn	Bn	**87a**	80%
84b	Ph[d]	*t*Bu	Bn	**87b**	77%
84d	Me	*t*Bu	Bn	**87d**	81%
84e	Ph	Bn	Bn	**87e**	87%
84f	H	*t*Bu	Bn	**87f**	Dec.

[a] Reactions conditions: 0.02 M substrate in 1,4-dioxane, 20 mole % $Yb(OTf)_3$, heated at 100°C in a sealed tube.

With the successful demonstration that acetylenic dienophiles were effective with Ugi based substrates, a series of IMDAF precursors were assembled through a Passerini MCR process. Addition of the three reagents to a solution of dichloromethane gave high yields of the Passerini products **88a-e** (Scheme 2.10).



Scheme 2.10 Synthesis of bicyclic lactones

However, attempts to convert the Passerini products to the oxabicyclo derivatives failed under thermal conditions. The starting materials were recovered unchanged after heating to 250°C, except with **88e** which underwent extensive decomposition. Surprisingly, the Lewis acid catalyzed reaction that had failed with the acetylenic amide series proved highly effective with the acetylenic esters. Treatment of the furans with Me_2AlCl delivered the Diels-Alder adducts **89a-d** in good yields, except with the terminal acetylene **88e**. As before, the reactions were highly selective, the stereochemistry of the cycloadducts provisionally assigned based on the x-ray structure of bridged bicycle **85c**. Unfortunately, attempts to directly convert the Passerini products to isobenzofuranones under ytterbium catalysis have not been successful.

Table 2.3. Sequential Passerini/IMDAF Studies

Entry (MCR)[a]	R1	R2	MCR Yield	Entry (IMDAF)[b]	IMDAF Yield[c]
88a	Me	Bn	86%	**89a**	77%
88b	Ph[d]	Bn	79%	**89b**	72%
88c	Ph[d]	*t*Bu	69%	**89c**	68%
88d	Me	*t*Bu	82%	**89d**	72%
88e	H	Bn	79%	**89e**	Dec.

[a] Reactions were run at a concentration of 0.2 M in CH_2Cl_2 at RT [b] a 0.2 M solution of the furan in CH_2Cl_2 was treated with Me_2AlCl at –78°C to RT. [c] Yields reported are for a pure diastereomer [d] All MCRs with phenyl propiolic acid were run in the dark to limit alkyne dimerization.

Conclusions

This striking difference in reactivity is quite interesting considering the small change from nitrogen to oxygen in the tether. Moreover, it was observed that the IMDAF derivatives from the Passerini reaction were much less stable then those derived from the Ugi products. The lactones quickly undergo retro Diels-Alder reaction at elevated temperatures while the lactams are completely stable. This may explain the failure to effect IMDAF reaction under thermal conditions with the acetylenic esters. In the lactam case, electron donation into the carbonyl carbon by the nitrogen lone pair is possible and more favorable than in the lactone case. In any event, greater instability of the lactones was also observed in the presence of acid. For example, a solution of the cycloadduct **89a** prepared in commercial $CDCl_3$ showed reversion to the starting furan within hours at RT while solutions in C_6D_6 are stable for at least one week. Protic acids have been reported in the literature to promote retro-IMDAF reactions of oxabicyclo[2.1.1]heptadiene derivatives to regenerate furan starting materials. In sharp contrast, the lactam derivatives do not show any propensity to undergo cycloreversion

under upon exposure to acidic conditions. Despite the structural similarities present in these two families of oxabicyclo[2.2.1]heptadiene derivatives, their reactivities and stabilities are quite different.

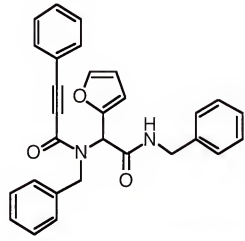
The sequential use of MCRs and cycloadditions can lead to structurally complex materials in short sequences. Utilizing Passerini and Ugi reactions in tandem with an IMDAF led to annulated oxabicyclo[2.2.1]heptadiene derivatives that are amenable to further elaboration. Studies on the conversion of the Passerini derivatives to analogs of viridin are currently under investigation.

Experimental Section

General methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury2000 at 300MHz and 75MHz respectively. Chemical shift (δ) are given in parts per million (ppm) and coupling constants (J), in hertz using TMS as an internal standard. The solvent was deuteriochloroform or deuteriobenzene where indicated. IR spectra were obtained as thin films between NaCl plates on a Perkin-Elmer 1600 series FTIR. The University of Florida Mass Spectroscopy Services performed all high-resolution mass spectra. All commercial materials were used without purification unless otherwise noted. The following solvents were distilled under positive pressure of dry argon: tetrahydrofuran (THF), diethyl ether (Et_2O) from sodium-benzophenone ketyl, methylene chloride (CH_2Cl_2) and toluene (C_6H_5-CH_3) from CaH_2. All the reactions were performed under an inert (Ar) atmosphere. Analytical thin-layer chromatography was performed using E. Merck silica 60-F254 coated 0.25-mm plates. Compounds were visualized by dipping the plates in an ammonium molybdate solution followed by heating. Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40-63 μm or 10-40 μm).

UGI Procedures and Results

3-Phenyl-propynoic acid benzyl-(benzylcarbamoyl-furan-2-yl-methyl)-amide



(84e) The following procedure is representative: to a flame dried 25 mL round bottomed flask containing MeOH (10 mL) and a magnetic stir bar was added distilled furfural (82 mg, 0.85 mmol) and benzyl amine (92 mg, 0.85 mmol). The solution was allowed to stir for *ca.* 20 mins or until solution turned light clear yellow. Phenyl propinoic acid (125 mg, 0.85 mmol) was added followed by benzyl isocyanide (100 mg, 0.85 mmol) and was allowed to stir at room temperature for 24-48 hours. Reaction was monitored by TLC (UV active) and quenched with saturated sodium bicarbonate solution (~2 mL). The organic layer was extracted with ethyl acetate (3 x 5 mL); combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (3:1, hexanes:ethyl acetate) to provide a white solid (341 mg, 89%).

Melting Point (uncorrected): 103-104°C.

IR 3301.35, 3063.20, 3031.21, 2931.12, 2214.41, 1682.48, 1622.85.

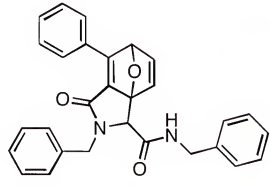
^{1}H NMR ($CDCl_3$, 300 MHz), δ 4.37 (dd, *J*=14.9, 6.1, 1H), 4.48 (dd, *J*=14.9, 6.1, 1H), 4.94 (d, *J*=16.5, 1H), 5.06 (d, *J*=16.5, 1H), 6.12 (s, 1H), 6.22 (dd, *J*= 3.2, 1.9, 1H), 6.36 (b, 1H), 6.54 (d, *J*=3.2, 1H), 7.2-7.6 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.9, 51.8, 55.8, 81.8, 91.8, 110.9, 112.7, 120.2, 126.9, 127.3, 127.6, 127.8, 128.1, 128.4, 128.6, 128.9, 129.2, 130.4, 132.7, 136.9, 137.8, 143.3, 147.1, 156.2, 166.9.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{29}H_{25}N_2O_3$ 449.1865, found 449.1874.

Anal. Calcd. for $C_{29}H_{25}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.61; H, 5.40; N, 6.33.

3-Benzyl-4-oxo-6-phenyl-10-oxa-3-aza-tricyclo[5.2.1.0]deca-5,8-diene-2-carboxylic acid benzylamide



(85e) To a flame dried 15-mL sealed glass tube, **84a** (50 mg, 0.11 mmol) was added to 8 ml of toluene. The solution was degassed by bubbling argon through the mixture for 5 min. The solution was heated to 260°C for 2.5 days. The reaction was monitored by TLC and toluene was removed in vacuo. The crude product was purified by flash

chromatography on silica gel (3:1, hexanes: ethyl acatate) to provide a white solid (42 mg, 84%).

Melting Point (uncorrected): 102-104°C.

IR 3316.51, 2918.46, 1689.17, 1685.33cm^{-1}.

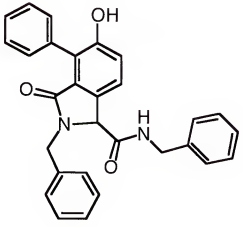
^{1}H NMR (500 MHz, $CDCl_3$,) δ 4.14 (d, *J*=14.8, 1H), 4.18 (s, 1H), 4.39 (dd, *J*=14.7, 5.7, 1H), 4.62 (dd, *J*=14.9, 5.9, 1H), 5.39 (d, *J*=14.8), 6.05 (s, 1H), 7.06 (d, *J*=5.4, 1H), 7.15 (dd, *J*=5.3, 2.0), 8.02 (d, *J*=7.6, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 43.9, 46.4, 62.2, 88.8, 94.6, 128.3, 128.7, 128.9 135.6, 137.4, 141.0, 141.8, 143.1, 158.5, 163.6, 166.9.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{29}H_{25}N_2O_3$ 449.1865, found 449.1866.

Anal. Calcd. for $C_{29}H_{25}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.68; H, 5.41; N, 6.38.

2-Benzyl-5-hydroxy-3-oxo-4-phenyl-2,3-dihydro-1*H*-isoindole-1-carboxylic acid benzylamide



(87e) To a flame dried 15 mL sealed glass tube, **84e** (50 mg, 0.11 mmol) and $Yb(OTf)_3$ (13 mg, 0.0223, mmol 20 mol %) were added to 5 ml 1,4-dioxane. The solution was degassed by bubbling argon through the mixture for 5 min. The solution was heated to 120°C for 5 hours. The reaction was monitored by TLC and solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel (3:1, hexanes: ethyl acetate) to provide an off white solid (43 mg, 87%).

Melting Point (uncorrected): 124-127°C.

IR 3292.59, 2962.75, 2917.36, 1671.34, 1663.67 cm^{-1}.

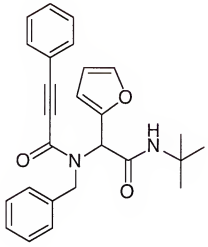
^{1}H NMR (300 MHz, $CDCl_3$,) δ 4.14 (d, *J*=14.8, 1H), 4.24 (dd, *J*=14.8, 5.7, 1H), 4.34 (dd, *J*=14.7, 5.9, 1H), 4.80 (s, 1H), 5.10 (d, *J*=14.8), 6.05 (s, 1H), 7.20 (d, *J*=5.7, 1H), 7.50 (d, *J*=5.9).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.6, 46.1, 63.0, 120.2, 123.5, 127.9, 128.9, 134.1, 136.2, 137.6, 154.2, 168.1, 168.8.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{29}H_{25}N_2O_3$ 449.1865, found 449.1881.

Anal. Calcd. for $C_{29}H_{25}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.64; H, 5.38; N, 6.22.

3-Phenyl-propynoic acid benzyl-(*tert*-butylcarbamoyl-furan-2-yl-methyl)-amide



(84b) Yield: 74%.

Melting Point (uncorrected): 127-128 .

IR 3313.8, 2968.7.2, 2213.4, 1678.8, 1630.1 cm^1.

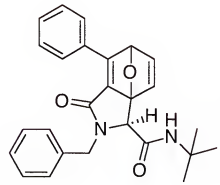
^{1}H NMR (300 MHz, $CDCl_3$) d 1.29 (s, 9H), 4.92 (dd, *J*=14.9, 6.1, 2H), 6.14 (s, 1H), 6.24 (dd, *J*=3.1, 1.6, 1H), 6.57 (d, *J*=3.1, 1H), 7.1-7.58 (multiplet).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.2, 42.1, 47.3, 63.2, 88.2, 97.1, 105.6, 110.7, 128.2, 129.1, 132.2, 142.7, 144.1, 153.1, 170.6.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{26}H_{26}N_2O_3$ 415.1977, found 415.2006.

Anal. Calcd. for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6,76. Found: C, 75.36; H, 6.31; N, 6.81.

3-Benzyl-4-oxo-6-phenyl-10-oxa-3-aza-tricyclo[5.2.1.00,0]deca-5,8-diene-2-carboxylic acid *tert*-butylamide



(85b) Yield: 81%.

Melting Point (uncorrected): 112-116°C.

IR 3297.1, 2921.5, 1681.7, 1655.2 cm^{-1}.

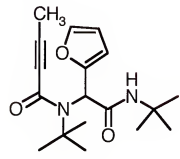
^{1}H NMR (300 MHz, $CDCl_3$) d 1.29 (s, 9H), 4.92 (dd, *J*=14.9, 6.1, 2H), 6.14 (s, 1H), 6.24 (dd, *J*=3.1, 1.6, 1H), 6.57 (d, *J*=3.1, 1H), 7.1-7.58 (multiplet).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.8, 41.8, 50.5, 68.1, 76.9, 127.4, 128.7, 134.9, 138.1, 146.9, 164.8, 176.2.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{26}H_{26}N_2O_3$ 415.1977, found 415.2032.

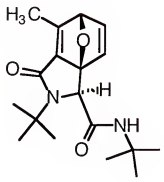
Anal. Calcd. for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6,76. Found: C, 75.51; H, 6.21; N, 6.63.

But-2-ynoic acid *tert*-butyl-(*tert*-butylcarbamoyl-furan-2-yl-methyl)-amide



(84c) The following procedure is representative: To a flame dried 25-mL round bottomed flask containing dry MeOH (10 mL) and a magnetic stir bar was added distilled furfural (231mg, 2.4 mmol) and *t*-butyl amine (257 mg, 2.4 mmol). The solution was allowed to stir for *ca.* 20 min or until the solution turned light clear yellow. Carboxylic acid (202 mg, 2.4 mmol) was added followed by isocyanide (274 mg, 2.4 mmol) and was allowed to stir at room temperature for 24-48 hours. Reaction was monitored by TLC and quenched with saturated sodium bicarbonate solution (~2 mL). The organic layer was extracted with ethyl acetate (3 x 5 mL); combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (3:1, hexanes:ethyl acetate) to provide a white solid (621 mg, 80%) which was determined to be the cycloadduct **85c**. IR N/A. ^{1}H NMR (300 MHz, $CDCl_3$,) N/A ^{13}C NMR $CDCl_3$ (75 MHz) δ N/A. HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{18}H_{27}N_2O_3$ 319.2022, found N/A.

3-*tert*-Butyl-6-methyl-4-oxo-10-oxa-3-aza-tricyclo[5.2.1.0]deca-5,8-diene-2-carboxylic acid *tert*-butylamide



(85c) Obtained from Ugi reaction **84c**.

Melting Point (uncorrected): 109-111

IR 3311.6, 2921.5, 2851.2, 1685.1, 1649.9 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.36 (s, 9H), 1.53 (s, 9H), 2.16 (s, 3H), 4.23 (s, 1H), 5.34 (d, *J*=1.90, 1H), 5.57 (s, 1H), 7.19 (dd, *J*=5.3, 2.08 ??, 1H), 7.14 (dd, 2.08, 1.90, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.50, 28.36, 28.81, 52.11, 56.78, 63.89, 68.64, 91.55, 142.36, 145.49, 157.99.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{18}H_{27}N_2O_3$ 319.2022, found 319.2020.

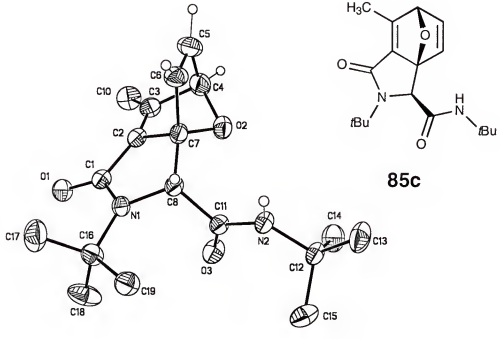
Anal. Calcd. for $C_{18}H_{27}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.91; H, 8.26; N, 8.91.

X-ray experimental: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK_a radiation (l = 0.71073 Å). Cell parameters were refined using up to 2844 reflections. A

hemisphere of data (1381 frames) was collected using the w-scan method (0.3∞ frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

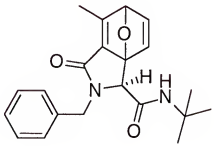
The structure was solved by the Direct Methods in *SHELXTL5*, and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms, except the N2 proton that was obtained from a Difference Fourier map and refined without any constraints. A total of 220 parameters were refined in the final cycle of refinement using 2191 reflections with $I > 2s(I)$ to yield R_1 and wR_2 of 4.71% and 9.78%, respectively. Refinement was done using F^2.

Sheldrick, G. M. (1998). *SHELXTL5*. Bruker-AXS, Madison, Wisconsin, USA.



85c

3-Benzyl-6-methyl-4-oxo-10-oxa-3-aza-tricyclo[5.2.1.00,0]deca-5,8-diene-2-carboxylic acid *tert*-butylamide



(85d) Yield: 78%.

Melting Point (uncorrected): 106-109°C.

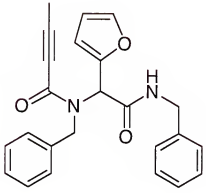
IR 3294.8, 2916.2, 1688.4, 1657.8 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) d 1.27 (s, 9H), 2.22 (s, 3H), 4.14 (d, *J*=14.7), 4.36 (s, 1H), 5.07 (d, *J*=14.7), 5.37 (d, *J*=2.1, 1H), 5.46 (b, 1H), 7.10 (dd, *J*= 2.1, 2.3, 1H), 7.27-7.37 (multiplet).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.7, 30.8, 41.7, 50.1, 68.2, 77.7, 85.1, 127.2, 129.2, 137.2, 143.6, 163.7, 175.4.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{21}H_{24}N_2O_3$ 353.1820, found 353.1856.

But-2-ynoic acid benzyl-(benzylcarbamoyl-furan-2-yl-methyl)-amide



(84a) Yield: 88% . Melting point:107-110°C.

IR 3317. 5, 1667.4, 1623.1 cm^{-1}.

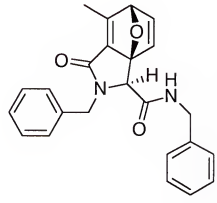
^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.8 (s, 3H), 4.32 (dd, *J*=3.2, 1.5, 2H), 4.81 (dd, *J*=15.7, 6.7, 2H), 5.94 (s, 1H), 6.18 (b, 1H), 6.22 (b, 1H), 6.41 (d, *J*=1.9, 1H), 7.2-7.6 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.8, 47.3, 48.0, 62.4, 78.2, 91.6, 105.7, 110.6, 127.3, 128.1, 137.7, 142.0, 144.5, 152.5, 177.2 .

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{24}H_{22}N_2O_3$ 387.1664, found 387.1700.

Anal. Calcd. for: $C_{24}H_{22}N_2O_3$ C, 74.59; H, 5.74; N, 7.25. Found: C, 74.47; H, 5.77; N, 7.29.

3-Benzyl-6-methyl-4-oxo-10-oxa-3-aza-tricyclo[5.2.1.00,0]deca-5,8-diene-2-carboxylic acid benzylamide



(85a) Yield: 74% .

Melting Point (uncorrected): 104-109°C.

IR 3301.7, 2872.1, 1684.6 cm^{-1}.

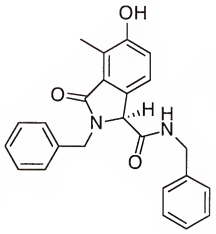
^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.22 (s, 3H), 4.31 (d, *J*=14.6, 1H), 4.39 (s, 1H), 4.46 (dd, *J*=13.9, 5.2, 1H), 4.68 (dd, *J*=13.9, 5.2, 1H), 5.43 (d, *J*=13.9), 6.05 (s, 1H), 7.2-7.6 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.8, 48.6, 50.5, 67.8, 77.2, 85.4, 127.1, 128.1, 137.2, 142.6, 163.6, 175.7.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{24}H_{22}N_2O_3$ 387.1664, found 387.1713.

Anal. Calcd. for: $C_{24}H_{22}N_2O_3$ C, 74.59; H, 5.74; N, 7.25. Found: C, 74.39; H, 5.54; N, 7.39.

2-Benzyl-5-hydroxy-4-methyl-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxylic acid benzylamide



(87a) Yield: 80% .

Melting Point (uncorrected): 121-127°C.

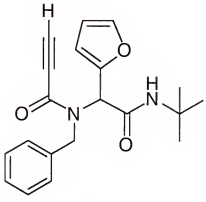
IR 3508.3, 2944.2, 2876.1, 1681.8, 1652.5 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.92 (s, 3H), 2.62, (s, 1H), 4.16 (d, *J*=14.7, 1H), 4.53 (d, *J*=5.7, 2H), 5.17 (d, *J*=14.7, 1H), 5.96 (b, 1H), 6.95 (d, *J*=8.1, 1H), 7.01(m, 2H), 7.2-7.3 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2, 51.2, 52.1, 68.9, 77.1, 84.8, 128.5, 128.9, 137.7, 143.2, 166.2, 176.3.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{24}H_{22}N_2O_3$ 387.1664, found 387.1727.

Propynoic acid benzyl-(*tert*-butylcarbamoyl-furan-2-yl-methyl)-amide



NOTE: Product obtained from TMS adduct. Yield: 85%.

Melting Point (uncorrected): 110-112°C;

IR 3322.2, 2969.0, 2104.5, 1673.8, 1667.4 cm^{-1}.

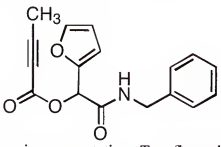
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.11 (s, 1H), 4.96 (dd, *J*= 15.8, 7.3, 2H), 4.96 (dd, *J*=3.1, 1.7, 1H), 6.23 (s, 1H), 6.54 (d, *J*=3.1, 1H), 6.73 (d, *J*=1.7, 1H) 7.02 (m, 5H).

^{13}C NMR $CDCl_3$ (75 MHz) δ 28.7, 47.4, 51.5, 52.0, 56.0, 80.1, 110.8, 111.0, 112.4,127.0,128.3, 128.6, 136.7, 143.2, 147.2, 165.8.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{20}H_{22}N_2O_3$ 339.1664, found 339.1743.

Passerini Procedure

But-2-ynoic acid benzylcarbamoyl-furan-2-yl-methyl ester



(88a) The following procedure is representative: To a flame dried 25-mL round bottomed flask containing CH_2Cl_2 (10 mL), and a magnetic stir bar was added distilled furfural (82 mg, 0.85 mmol). Carboxylic acid (75 mg, 0.85 mmol) and isocyanide (100 mg, 0.85 mmol) were added to the reaction which was allowed to stir at room temperature for 24-72 hours. The reaction was monitored by TLC and quenched with saturated sodium bicarbonate (2 mL). The organic layer was extracted with ethyl acetate (3 x 5 mL); combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (3:1, hexanes:ethyl acetate) to provide a white solid (218 mg, 86%).

Melting Point (uncorrected): 103-104°C.

IR 3301.4, 2921.8, 2239.1, 1716.3, 1676.3, 1235.9 cm^{-1}.

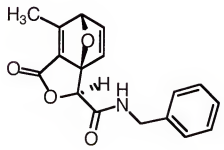
^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.9 (s, 3H), 4.55 (dd, 14.9, 5.9, 2H), 6.3 (s, 1H), 6.38 (m, 1H), 6.55 (d, *J*= 2.1, 1H), 6.71 (b, 1H), 7.29-7.39 (m, 5H), 7.42 (d, *J*=2.1, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz)δ 43.7, 69.7, 105.2, 110.9, 112.3, 143.9, 147.4, 151.4, 179.1.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{17}H_{16}NO_4$ 298.1079, found 298.1082.

Anal. Calcd. for $C_{17}H_{16}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.74; H, 4.98; N, 4.77.

6-Methyl-4-oxo-3,10-dioxa-tricyclo[5.2.1.0]deca-5,8-diene-2-carboxylic acid benzylamide



(89a) The following procedure is representative: to a flame dried 25 mL round bottomed flask containing CH_2Cl_2 (10 mL) and a magnetic stir bar was added **88a** (50 mg, 0.17 mmol). The solution was cooled to –75 °C and $MeAlCl_2$ (1M in hexanes, 180 μL, 0.18 mmol) was added slowly and the solution was allowed to stir for 1.5 h. Saturated sodium bicarbonate (2 mL) was added, and the mixture was allowed to stir for 5 min before extracting with CH_2Cl_2 (3 X 5 mL). The yellow liquid was allowed to evaporate in vacuo without heating. The crude semi-solid was purified by flash column chromatography on silica gel (1:1, hexanes:ethyl acetate) to provide a white solid (42 mg, 82%). Melting point, 102-103°C .

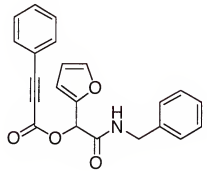
IR 3313,3, 3069.6, 2966.3, 1692,4, 1647.5 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6,) δ 2.01 (s, 3H), 4.56 (dd, *J*=14.7, 5.9, 2H), 5.22 (s, 1H), 6.41 (d, *J*=2.1, 1H), 6.52 (d, *J*= 2.1, 1H), 7.15 (s, 1H), 7.3 (m, 5H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.3, 47.7, 72.1, 109.1, 114.6, 116.2, 145.8, 149.1, 155.2, 178.5. HRMS

(LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{17}H_{16}NO_4$ 298.1079, found 298.1095.

Phenyl-propynoic acid benzylcarbamoyl-furan-2-yl-methyl ester



(88b) Yield: 79%.

Melting Point (uncorrected): 105-107°C.

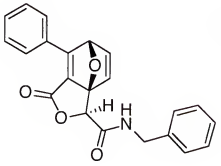
IR 3300.9, 3031.5, 2929.8, 2215.9, 1716.6, 1690.6 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 4.2 (dd, *J*=14.4, 5.6, 2H), 5.9 (d, *J*=3.2, 1H), 6.3 (b, 1H), 6.4 (d, *J*=3.2, 1H), 6.5 (s, 1H), 7.2-7.6 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.01,81.2, 86.3, 88.3, 107.9, 110.7, 122.3, 127.1, 128.6, 132.3, 142, 155.6, 172.8. HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{22}H_{17}NO_4$ 360.1191, found 360.1210.

Anal. Calcd. for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.61; H, 4.71; N, 3.87.

4-Oxo-6-phenyl-3,10-dioxa-tricyclo[5.2.1.00,0]deca-5,8-diene-2-carboxylic acid benzylamide



(89b) Yield: 72%.

Melting Point (uncorrected): 101-103°C.

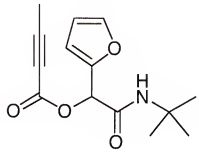
IR 2922.9, 2853.4, 1831.9, 1775.7 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 4.2 (dd, *J*=14.1, 5.2, 2H), 5.2 (b, 1H), 5.5 (d, *J*=3.6, 1H), 6.2 (d, *J*=3.6, 1H), 6.7 (s, 1H), 7.4-7.6 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.05, 87.3, 87.7, 89.2, 105.3, 110.2, 123.7, 127.6, 128.8, 134.1, 142.2, 157.8, 171.6.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{22}H_{17}NO_4$ 360.1191, found 360.1181.

But-2-ynoic acid *tert*-butylcarbamoyl-furan-2-yl-methyl ester



(88d) Yield: 82%.

Melting Point (uncorrected): 104-107°C.

IR 3283.8, 2968.7, 2238.3, 1718.7, 1675.1 cm^{-1}.

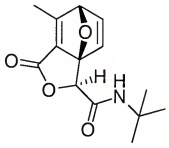
^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.34 (s, 9H), 2.0 (s, 3H), 6.05 (b, 1H), 6.11 (s, 1H), 6.36 (dd, *J*=3.4, 1.9, 1H), 6.5 (d, *J*=3.4,1H), 7.4 (dd, *J*= 0.75, 1.9, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.12, 28.8, 52.1, 69.9, 88.3, 110.8, 111.9, 143.8, 147.9, 151.7, 164.3.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{14}H_{17}NO_4$ 264.1191, found 264.1229.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.01; H, 6.41; N, 5.52.

6-Methyl-4-oxo-3,10-dioxa-tricyclo[5.2.1.00,0]deca-5,8-diene-2-carboxylic acid *tert*-butylamide



(89d) Yield: 72%.

Melting Point (uncorrected):: 101-105°C.

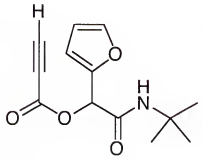
IR 3028.1 2844.6, 1707.6, 1662.3 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6,) δ 1.0 (s, 3H), 1.4 (s, 9H), 5.1 (s, 1H), 5.33 (dd, *J*=5.83, 1.37 , 1H), 5.47 (d, *J*=5.83,1H), 5.58 (d, *J*= 1.37, 1H), 6.6 (s, 1H), 6.9 (b, 1H).

^{13}C NMR (C_6D_6, 75 MHz) δ 3.1, 29.3, 51.2, 88.5, 102.3, 130.8, 130.9, 160.1, 164.1

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{14}H_{17}NO_4$ 264.1191, found 264.1227.

Propynoic acid *tert*-butylcarbamoyl-furan-2-yl-methyl ester



(88e) Yield: 79%.

Melting Point (uncorrected): 104-107°C.

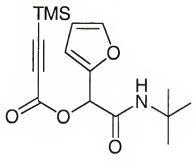
IR 2962.7, 2894.2, 2108.6, 1711.6, 1671.5 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6,) δ 1.3 (s, 9H), 2.8 (s, 1H), 5.8 (b, 1H), 6.2 (s, 1H), 6.28 (dd, *J*=3.1, 1.7, 1H) 6.5 (d, *J*= 1.7, 1H), 7.3 (d, *J*= 1.7, 1H).

^{13}C NMR (C_6D_6, 75 MHz) δ 30.1, 41.0, 75.1, 87.2, 107.9, 110.7, 142.1, 143.8, 154.2, 170.3.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{13}H_{15}NO_4$ 250.1137 found 250.12

(Trimethyl-silanyl)-propynoic acid *tert*-butylcarbamoyl-furan-2-yl-methyl ester



Yield: 65%.

Melting Point (uncorrected): 114-118°C.

IR 2922.9, 2853.4, 1831.9, 1775.7 cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6,) δ 0.85 (s, 9H), 1.13 (s, 9H), 5.82 (b, 1H), 5.90 (dd, 1.9, 3.1, 1H), 6.33 (s, 1H) 6.38 (d, *J*= 3.8, 1H), 6.93 (d, *J*= 1.7, 1H).

^{13}C NMR (C_6D_6, 75 MHz) δ -12.2, 42.1, 77.5, 88.1, 106.1, 111.5, 141.0, 142.3, 155.3, 172.8.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{16}H_{23}NO_4Si$ 322.1430 found 322.1442.

CHAPTER 3
A MULTICOMPONENT REACTION APPROACH TO THE SYNTHESIS OF HIGHLY DIVERSE POLYMERS WITH POLYPEPTIDE-LIKE FEATURES

The principals of diversity-driven synthesis have found wide application for the synthesis of small molecules with potential as new therapeutic agents,[50] catalysts[51] and ligands.[52] One of the most practical routes is to employ a parallel synthetic strategy whereby large collections of molecules with known variations in structures are prepared as distinct chemical entities and then screened for a particular property. Although these techniques are widely accepted in small molecule synthesis, the application of these methods for the synthesis of macromolecules and materials has been less explored.[53] Oligopeptides of great diversity have been prepared[54] by the stepwise condensation of natural building blocks. There have also been some efforts[55] aimed at the diversification of polymers by the use of diversity-generating reactions on a pre-existing macromolecular scaffold. We have been interested in developing an approach for the diversity driven synthesis of new materials through a strategy whereby highly functionalized and diversified monomers are prepared in a parallel fashion and then converted to macromolecules in a single polymerization step. Herein we report our initial investigations for the synthesis of highly diverse polymeric materials.[56]

Results and Discussion

In formulating a strategy we focused on devising a method that would (1) allow rapid access to monomers from readily available starting materials, (2) be amenable to structural diversification and (3) be tolerant of a wide range of functionality. In considering these requirements, it was clear that a two-step reaction sequence involving monomer preparation and then polymerization would offer the most direct entry into these new materials. For the initial step of the sequence we were attracted to the use of a multi-component reaction[57] (MCR) to generate a variety of monomers in a parallel fashion and in a single step. The Ugi 4CC reaction[58] seemed particularly attractive for this process since it can be used to unite four separate units into a single molecule. If one of these four subunits possessed functionality that could be used in a polymerization reaction, new materials would result. In addition to the ease and potential diversity offered by the Ugi 4CC, we were also interested in the similarity of the Ugi products to peptides and envisioned that macromolecules constructed from these types of monomers would have physical properties reminiscent of polypeptides and proteins. This suggests possible application of these materials as catalysts[69] or biomaterials.[60] In addition to the structural diversity brought about by varying the components, the position of attachment to the polymer backbone could also be varied (Figure 6).

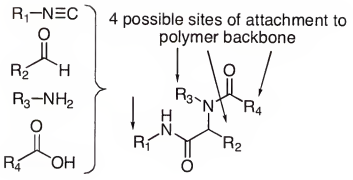
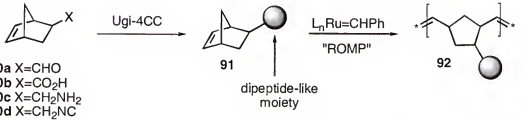


Figure 6. Polymers derived from an Ugi 4CC Product

The other component of this diversity-generating strategy is the choice of polymerization strategy. Although there are many possibilities for polymerization, we were concerned that the method of polymerization must be compatible with the highly polar functionality found in the Ugi products. We were attracted to the application of metathesis-based reactions[61] since the recent preparation of well-defined metathesis catalysts are known to be highly tolerant of a wide range of functionality. In particular the ring-opening metathesis polymerization[62] (ROMP) of functionalized norbornenes would offer quick access to new polymers (Scheme 3.1).



Scheme 3.1: An Ugi 4CC/ROMP Strategy for Diversity-Driven Polymer Synthesis

Four polymer types are available (see Figure 1) depending on which norbornene component is used. We considered components **90a-d** for use in the MCR/ROMP

strategy, but we have limited our current studies to **90a** and **90b**, which are commercially available. Components **90c** and **90d** are known[63] and can be prepared easily. Ugi 4CC with one of these components would generate the highly functionalized monomers **91** which, upon exposure to an olefin metathesis catalyst, would trigger ROMP to produce the peptide-like polymers **92**.

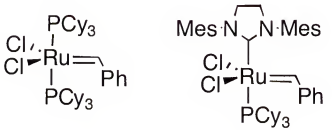
Our initial studies were focused on evaluating the ability of **90a** and **90b** in the Ugi 4CC reaction and the ability of these products to be effectively polymerized by Grubbs' catalyst. Four MCR derived monomers, **93a-d**, were prepared for evaluation in very good yield simply by stirring the four components overnight in methanol (Table 3.1).

Table 3.1. Synthesis of Monomers by Ugi 4CC Reaction

Entry[a]	Aldehyde[b]	Acid[b]	Amine	Isonitrile	Yield[c]
93a					75 %
93b					71 %
93c					73 %
93d					72%

(a) Reaction conditions: 1 equivalent of each component was dissolved in anhydrous methanol and stirred for 24 hrs. at room temperature (b) Mixture of *exo* and *endo* (80:20) isomers used (c)Yield refers to isolated yield after chromatography

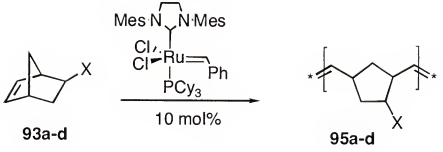
With monomers **93a-d** readily available, we next examined the conversion of these compound into polymeric structures with Grubbs' catalysts **94a** and **94b** (Figure 7).



94a **94b**

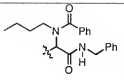
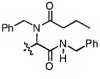
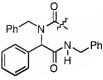
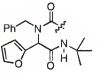
Figure 7. Ruthenium catalysts for ROMP reaction.

Initial experiments with the first generation Grubbs catalyst **94a**[64] were disappointing. Very little conversion to polymeric materials was observed and only very small oligomers could be isolated after elevated catalyst loading and prolonged reaction times. The sluggish behavior of the catalyst in these reactions was attributed to inhibition by the polar functionality in the monomer. Recourse was made to the second generation catalyst **94b**[65] which is known to be more tolerant of heteroatom functionality. A series of optimization experiments indicated that 10 mole % of catalyst **94b** added to a concentrated solution of the monomers in dichloromethane efficiently produced the corresponding polymers (Table 3.2).



Scheme 3.2: Polymerization of Ugi products

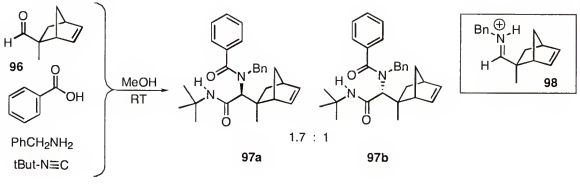
Table 3.2. Synthesis of Polymers by ROMP Reaction

Polymer[a]	X	Yield[b]	Mw[c]	PDI[c]	Tg[d]
95a		84 %	47560	2.03	137°
95b		64%	49443	1.29	143°
95c		85%	36375	1.41	169°
95d		72%	22320	1.37	Decomp.

(a) Reaction conditions: 0.5 M monomer in CH_2Cl_2 treated with 10 mol % catalyst **94b** (b) After precipitation of the polymer from ethyl acetate:hexanes (c) determined by gel permeation chromatography (d) determined by differential scanning calorimetry, average of two determinations.

Polymerization of these monomers under the optimized conditions gave good yields of polymers with relatively high molecular weights and narrow dispersities as is characteristic of ROMP based polymerizations. Determination of the glass transition temperature revealed that the polymers were highly crystalline in nature, consistent with a high degree of hydrogen bonding within the polymer.

With the successful synthesis of these highly functionalized and easily diversified polymers our attention turned to potential application of these new compounds. The previously described polymers may function as new materials or possibly as metal binding agents. However, we were most interested in the application of these types of compounds as catalysts in asymmetric reactions or materials for chiral separations. Peptide based catalysts have recently become very popular as sources of new entities for asymmetric transformations. In order to use these compounds in this capacity, it would be necessary to prepare the monomers in enantiomerically pure form. There is little work currently available on the enantioselective Ugi 4CC reaction. However, since the norbornene scaffold contains a pre-existing stereocenter there was the possibility for a diastereoselective MCR on a chiral norbornene derivative. An asymmetric Diels-Alder reaction between cyclopentadiene and methyl acrolein as described by Corey[66] provided direct and efficient access to chiral norbornene aldehyde derivative **96** for use in the Ugi 4CC reaction. It was felt that it may be possible to see some levels of diastereoselection which would be set by a facially selective addition to the intermediate iminium ion **98** (Scheme 3.3).



Scheme 3.3: Diastereoselective Ugi 4CC Reaction.

Unfortunately, Ugi reaction with enantiomerically enriched **96** (>92% ee) with benzoic acid, benzyl amine and *t*-butyl isocyanide showed very little diastereoselection, producing a mixture of isomers **97a** and **97b** in a 1.7:1 ratio. It appears that there is little selectivity on the attack by the isocyanide on iminium ion **98**. Although we were unable

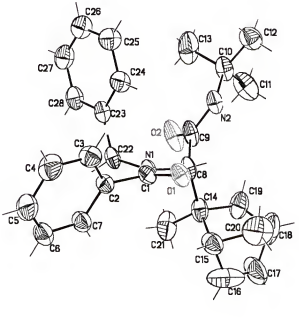
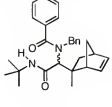
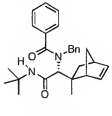
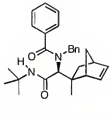


Figure 8. X-ray crystallographic of **97a**

to effect a highly selective reaction, it was fortunate that the two diastereomers were easily separated to produce the pure diastereomers. The identity of the major isomer was assigned by an x-ray crystal structure (Figure 8).

With these chiral monomers in hand, we were able to examine the conversion of these materials to the corresponding polymers both as diastereomeric mixtures (to produce a co-polymer) and as individual diastereomers (Table 3.3).

Table 3.3. Synthesis of Chiral Polymers by MCR/ROMP Sequence.

Polymer[a]	Monomer	$[a]^{25}_D$ monomer[b]	$[a]^{25}_D$ polymer[b]	Yield[c]	MW[d]	PDI[d]
99a		5.5°	-6.2 °	87%	21540	1.17
99b		21.1°	-46.0 °	88%	10740	1.15
99c		37.7°	-11.1 °	82%	13890	1.16

(a) Reaction conditions: 0.5 M monomer in CH_2Cl_2 treated with 10 mol % catalyst **94b** (b) determined in dichloromethane (c) after precipitation of the polymer from ethyl acetate:hexanes (d) determined by dynamic light scattering

The polymerization of the chiral monomers, both as individual diastereomers and as a mixture revealed some interesting selectivities. Polymerization of the mixture (which produces a co-polymer) gave polymers of much higher molecular weights than polymerization of the individual diastereomers. The polydispersities were uniform and narrow. Interestingly, the specific rotations of the polymers changed signs from the monomers, possibly indicating important secondary structure in the polymers.

Conclusion

We have been able to develop a strategy for the parallel synthesis of new materials by the sequential application of an Ugi 4CC and ROMP polymerizations. Other variations of this strategy should be possible and could lead to a large variety of new materials. This strategy has led to several new polymeric materials with unique chemical structures. We have also been able to extend this to the synthesis of chiral materials by using an enantiomerically pure aldehyde in the MCR reaction. Future efforts are directed towards the study of these chiral materials for asymmetric catalysis and for chiral separations.

General Reagents for the Synthesis of Monomers and Polymers

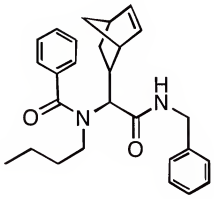
Methylene chloride was distilled from CaH_2. Methanol was dried over 4Å molecular sieves and used without further purification. Glassware used in the reactions was dried overnight in an oven at 165 °C. All reactions were performed under an atmosphere of argon unless noted otherwise. Amine, aldehyde, isocyanide and acid components were purchased from Aldrich and used as received. Catalyst **94b** was purchased from Strem chemical company

General Procedure for Preparation of Monomers [93a-d], [97a, 97b]

A 25 mL round bottom flask, under argon, equipped with a magnetic stir bar was charged with dry methanol (5.24 mL) and the aldehyde component (3.67 mmol). If the aldehyde was insoluble in methanol, dry methylene chloride was added dropwise to the methanol-aldehyde mixture until a homogeneous solution was obtained. The amine component (3.67 mmol) was then added to the reaction flask and the mixture was stirred for 20 min at room temperature. The acid component (3.67 mmol) was added, followed by the isocyanide component (3.67 mmol) 5 min later. The mixture was stirred for 24 hours at room temperature. Upon completion, solvents were removed under reduced pressure to give an oily residue. The residue was dissolved in the minimal volume of ethyl acetate (ca. 15 mL) and washed with saturated $NaHCO_3$ (3 x 10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield an oily residue. The residue was purified via column chromatography (75:25 hexane:ethyl acetate). Analytical samples were prepared by recrystallization from 95% ethanol and water mixture.

Chemical Characteristics of Representative Compounds

N-(Benzylcarbamoyl-bicyclo[2.2.1]hept-5-en-2-yl-methyl)-*N*-butyl-benzamide



[93a] Yield: 75%.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 0.81-1.12 (m, 9H), 1.2 (b, 2H), 1.65 (m, 4h), 3.35 (b, 2H), 4.48 (m, 4H), 5.90 (d, *J*=2.1,1H), 6.22 (dd, *J*= 5.4 and 3.1, 2H), 7.2-7.6 (m).

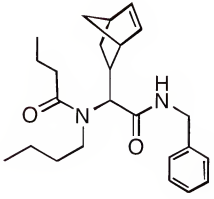
^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.1, 19.7, 33.1, 37.6, 42.3, 42.5, 43.4, 44.3, 50.3, 55.2, 127.4, 128.7, 132.7, 138.5, 143.3, 144.4, 167.2, 170.4.

IR (KBr plate); 3308.33, 3087.11, 2977.15, 1621.80, 1691.11 cm^{-1}.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{27}H_{33}N_2O_2$ 417.2542, found 417.2527.

Anal. Calcd. for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6,73. Found: C, 77.91; H, 7.93; N, 6.70.

N-(Benzylcarbamoyl-bicyclo[2.2.1]hept-5-en-2-yl-methyl)-*N*-butyl-butyramide



[93b] Yield: 71%.

^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.20 (m, 15H), 1.60 (m, 2H), 1.95 (m, 4H), 2.55 (m, 6H), 3.18 (b, 2H), 4.67 (m, 4H), 6.05 (b, 1H), 6.45 (dd, *J*= 4.8 and 2.4, 2H), 7.3-7.6 (m).

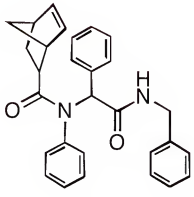
^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 18.7, 22.1, 31.4, 34.5, 42.3, 46.7, 57.9, 60.2, 124.2, 125.7, 128.4, 136.2, 144.2, 169.2, 172.7.

IR (KBr plate); 3301.21, 3015.20, 3086.32, 2911.02, 1677.30, 1602.14 cm^{-1}.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{24}H_{35}N_2O_2$ 383.2699, found 383.2676.

Anal. Calcd. for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.55; H, 8.83; N, 7.54.

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (benzylcarbamoyl-phenyl-methyl)-phenyl-amide



[93c] Yield:73%.

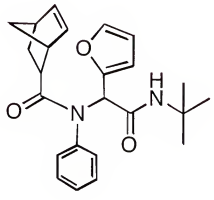
^{1}H NMR (300 MHz, $CDCl_3$,) δ 1.34 (b, 2H), 1.42 (b, 2H), 2.88 (b, 2H), 4.31 (bm, 4H), 5.88 (b, 1H), 6.25 (dd, 2H), 6.88 (b, 3H), 7.2-7.4 (m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.1, 39.2, 46.3, 47.3, 49.2, 126.2, 128.7, 129.4, 137.2, 164.7, 170.4. IR (KBr plate); 3308.33, 3012.10, 2914.33, 1633.10, 1685.21 cm^{-1}.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{30}H_{31}N_2O_2$ 451.2386, found 451.2319.

Anal. Calcd. for $C_{30}H_{30}N_2O_2$: C, 79.97; H, 6.89; N, 6.22. Found: C, 80.08; H, 6.89; N, 6.22.

Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (*tert*-butylcarbamoyl-furan-2-yl-methyl)-phenyl-amide



[93d] Yield: 72%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.88 (dd, 2H), 4.92 (dd, 2H), 5.98, (b, 1H), 6.21 (m, 1H), 6.54 (m, 1H), 6.57 (s, 1H), 7.1-7.38 (multiplet).

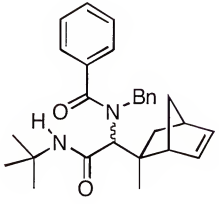
^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.6, 42.3, 42.5, 43.4, 44.3, 45.3, 49.2, 110.4, 127.5, 127.7, 127.8, 128.7, 128.8, 132.0, 132.7, 135.9, 137.1, 138.5, 138.6, 143.3, 144.3, 156.4, 171.2, 175.3.

IR (KBr plate); 3313.81, 2968.72, 2213.43, 1678.81, 1630.15 cm^{-1}.

HRMS (LSIMS POS, M+1) *m/z* (M^+) calculated for $C_{25}H_{31}N_2O_3$ 407.2335, found 407.2366.

Anal. Calcd. for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 74.12; H, 7.71; N, 6.54.

N-Benzyl-*N*-[*tert*-butylcarbamoyl-(2-methyl-bicyclo[2.2.1]hept-5-en-2-yl)-methyl]-benzamide



[97] Yield: 91%.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.00-7.40 (m, 10H), 6.80-7.00 (s, 1H), 6.40 (bs, 1H), 6.00-6.30 (m, 2H), 5.10-5.50 (m, 2H), 2.80-3.00 (m, 2H), 1.90 (bs, 1H), 1.40-1.90 (m, 2H), 1.18 (s, 3H), 1.00-1.10 (m, 9H), 0.80-1.00 (d, 1H).

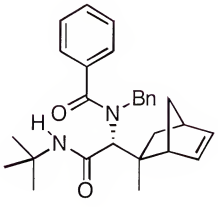
^{13}C NMR (CDCl$_3$, 300 MHz) δ 174.80, 169.164, 137.634, 137.347 , 135.751, 128.519, 128.513, 128.366, 126.870, 126.650, 126.550, 51.578, 51.378, 48.660, 43.946, 43.719, 28.522, 28.375, 28.281.

IR (KBr plate); 3310.01, 1675.14, 1602.30, 1547.21 cm^{-1}.

HRMS (LSIMS POS, M+1) m/z (M^+) calculated for $C_{28}H_{34}N_2O_2$, 431.2621; found, 431.2682.

Anal. Calcd. For $C_{28}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.06; H, 7.98; N, 6.48.

N-Benzyl-*N*-[*tert*-butylcarbamoyl-(2-methyl-bicyclo[2.2.1]hept-5-en-2-yl)-methyl]-benzamide

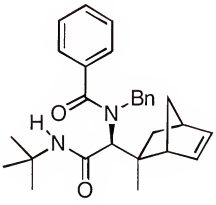


[97a] Yield: 80%.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00-7.50 (m, 10H), 6.80-7.00 (bs, 2H), 6.30-6.50 (bs, 1H), 6.00-6.20 (m, 2H), 5.20-5.30 (m, 1H), 2.74-2.90 (bs, 2H), 2.00-2.16 (bs, 1H), 1.64-1.80 (bs, 1H), 1.56-1.64 (s, 3H), 1.00-1.40 (bs, 9H), 0.82-0.94 (bs, 2H).

HRMS (LSIMS POS, M+1) m/z (M^+) calculated for $C_{28}H_{34}N_2O_2$, 431.2621; found, 431.2699.

N-Benzyl-*N*-[*tert*-butylcarbamoyl-(2-methyl-bicyclo[2.2.1]hept-5-en-2-yl)-methyl]-benzamide



(99b) Yield: 82%.

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.00-7.40 (m, 10H), 6.80-7.00 (bs, 2H), 6.50 (bs, 1H), 6.00-6.30 (m, 2H), 5.20-5.40 (m, 1H), 2.60-2.90 (m, 2H), 1.77-1.85 (m, 1H), 1.60-1.74 (m, 2H), 1.32-1.40 (bs, 3H), 1.10-1.20 (m, 9H), 1.00-1.08 (dd, 1H).

^{13}C NMR (CDCl$_3$, 300 MHz) δ 169.175, 138.07, 137.498, 129.666, 128.524, 126.862, 51.663, 48.451, 43.851, 28.526.

HRMS (LSIMS POS, M+1) m/z (M^+) calculated for $C_{28}H_{34}N_2O_2$, 431.2621; found, 431.2700.

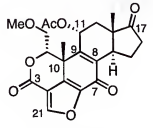
General Procedure for the Synthesis of ROMP Polymers [95a-d], [99a-c]

A 30 mL sealed glass tube was purged with argon and charged with dry methylene chloride (0.5 mL) and monomer (0.232 mmol). Upon dissolution of monomer, catalyst **94b** (0.0348 mmol) was added and the glass tube was sealed tightly. The glass tube was then immersed in an oil bath at 55°C. The reaction was monitored by thin layer chromatography and showed complete consumption of monomer after approximately 15 min. The sealed tube was allowed to cool to room temperature and ethyl vinyl ether (0.5 mL) was added to the reaction mixture. The reaction mixture was left to stand for an additional 10 minutes, after which the contents of the tube were transferred to a 50 mL round bottom flask and concentrated *in vacuo* to yield a brown foamy residue. The residue was dissolved in the minimal volume of ethyl acetate (ca. 10 mL) and transferred to a 100 mL beaker. The beaker and solution were cooled in an ice bath for 10 min before hexane (75 mL) was added to the solution to precipitate the polymer. The polymer was collected on a medium glass frit by suction filtration and dried under vacuum for several hours.

Polymers. Peaks in ^{1}H NMR spectrum for each polymer were broad and as a result were identical. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.50-7.50, 4.70-5.70, 4.00-4.60, 2.05-3.60, 1.80-2.00, 0.40-1.30. IR (KBr plate); 3301.10, 1672.21, 1612.21, 1530.56 cm^{-1}.

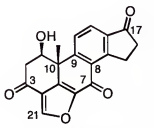
CHAPTER 4
A COUPLING AND CLAISEN REARANGEMENT APPROACH TO THE SYNTHESIS OF VIRIDIN

The majority of our initial efforts have focused on the synthesis of viridin and wortmannin analogs. We have also examined two independent routes toward the total synthesis that focus on early formation of the synthetically challenging C9-C10 linkage. The chiral quaternary position at C10 poses an interesting challenge in the total synthesis of the viridin and wortmannin. We decided to attack this key feature early in the synthesis and design the rest of the synthetic approach around this stereocenter. We decided to use a convergent approach in both routes, relying on a coupling and a rearrangement reaction to assemble the C9-C10 linkage.



wortmannin

100

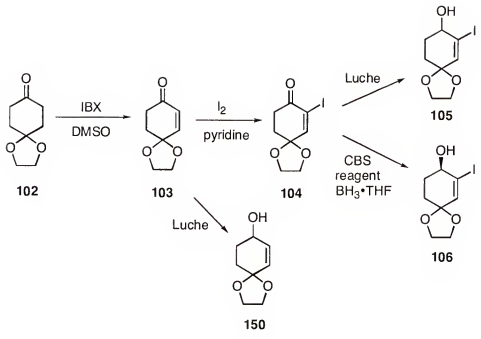


demethoxyviridin

101

Suzuki Coupling Approach

One of the strategies we explored is the preparation of a chiral A-ring synthon to be coupled to an appropriate aryl moiety via a Suzuki coupling. The configuration of the C10 quaternary center could be controlled by induction from the center at C1, prepared by an asymmetric reduction reaction (Scheme 4.1).



Scheme 4.1: Synthesis of A-ring synthon

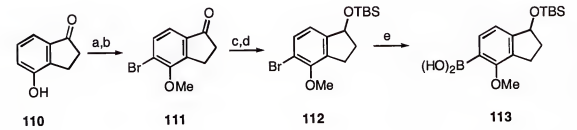
The racemic A-ring precursor **105** was prepared first, in order to study the coupling conditions, from the commercially available ketal **102**. Oxidation to the enone **103** was achieved by oxidation with IBX.[67] Iodination of the enone at the α-position sets up one of the cross-coupling components, **104**. Alternatively, configuration of the secondary hydroxyl group at C1 can be controlled in a chiral fashion by use of (±)-CBS reagent.[68] The chiral reduction works very well to yield **106** in greater than 80% yield. However, in both cases, the compound decomposes upon heating or contact with trace acid.

We decided to couple **104** to a model aromatic moiety in order to once again study the reactions conditions. As a model for the aromatic C-ring moiety, *o*-methoxy phenylboronic acid was employed in a palladium catalyzed Suzuki coupling reaction[69] to give **107** in very high yield. To complete the construction of the quaternary carbon, we examined the use of a Stork silyl-tethered radical[70] to install the C10 methyl group. This strategy utilizes the intramolecular delivery of a carbon atom to C10 in

Scheme 4.2: Construction of C10 center

a stereoselective fashion. Reduction of **107** followed by silylation of the C1 alcohol gives **108**. Addition of tin hydride should promote a 5-exo radical cyclization to give **109**. Use of the chiral alcohol **106** would allow for a selective cis-ring closure and stereoselective setting of the C10 methyl. Desilylation of the siloxane should liberate the C1 hydroxyl and the C10 methyl group. Further work on the radical is currently being examined.

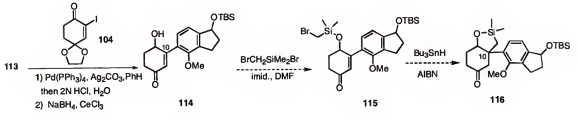
We have made nice progress toward this approach, as the key to this strategy is the union of the two fragments, and the radical cyclization to install the angular methyl group at C10. For the synthesis, we will prepare the CD-ring boronate ester from commercially available indanone **110** (Scheme 4.3).



Scheme 4.3: Synthesis of CD-ring Boronate. Key: (a) *t*BuNH$_2$, Br$_2$ (b) NaOH, Me_2SO_4 (c) $NaBH_4$ (d) TBSCl, imid. (e) *n*BuLi, B(OiPr)$_3$ then HCl(aq)

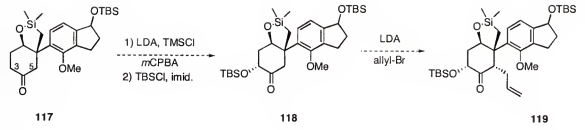
It was necessary to prepare boronic acid **113** as the coupling partner needed in the natural product. Ortho-bromination of 4-hydroxyindanone **110** followed by protection of the phenolic oxygen **111** via dimethylsulfate and potassium carbonate proceeded in

excellent yields. $NaBH_4$ reduction of the ketone and subsequent TBS protection of the resulting alcohol were achieved to yield **112** in 83% overall yield for the two steps.[71] It is important to note that initial attempts to protect ketone **110** as a the ketal were unsuccessful due to solubility problems of the hydroxy indanone. Synthesis of the boronate **113** proved difficult under normal conditions with only 32% of the desired product obtained. Other conditions to form the boronic acid need to be investigated.



Scheme 4.4: Proposed Suzuki coupling approach

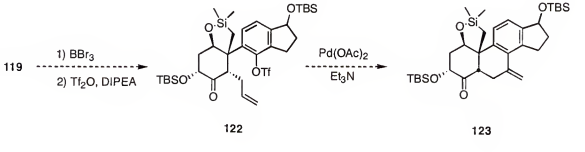
Palladium catalyzed coupling of **113** and iodide **105** should proceed as in model studies to yield alcohol **114**. Introduction of the C9-methyl group will be effected through a silyl-tethered radical from the C1 carbinol to give siloxane **115**. We expect that radical cyclization **116** under stereoselective conditions will occur to give a predominance of the cis isomer, thus setting the desired syn relationship between the C1 alcohol and the C10 methyl groups. The next stage of the synthesis will focus on functionalization of ring-A and closure of the central B-ring. Functionalization of the A-ring will rely on stepwise enolate generation on the two carbons flanking the carbonyl (Scheme 4.5).



Scheme 4.5: Functionalization of ring A

Utilizing the chiral alcohol **106**, we can approach a stereoselective functionalization of ring A and closure of ring B. The protons at C3 and C5 should have different kinetic acidities owing to the adjacent quaternary center at C10. A large base such as LDA should preferentially abstract the C3 proton followed by trapping as the corresponding silyl enol-ether. Oxidation of the silyl enol-ether, protection and allylation at the C5 position would give **119.**

Intermediate **119** contains 18 of the 19 carbons of the natural product and 3 of the 5 ring systems. The next important goal in the synthesis of the natural product would be the formation of ring-B though a second palladium catalyzed reaction (Scheme 4.6).

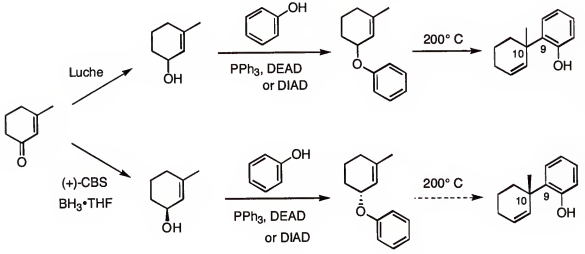


Scheme 4.6: Heck closure of B-ring

Conversion of the phenolic methyl ether **119** to the aryl triflate, **122**, sets the stage for B-ring closure through a Heck cyclization. Exposure of the triflate to a palladium catalyst should result in a selective 6-exo trig closure to yield tetracycle **123**.

Claisen Rearrangement Approach to Viridin Analog

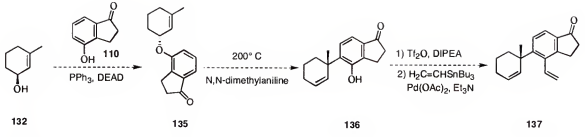
Another route developed in conjunction with the above approach involves a coupling reaction followed by a Claisen rearrangement to set the C9 quaternary center (Scheme 4.7). The configuration of the quaternary carbon can be established during construction of the C9-C10 bond if the chiral alcohol **132** is employed.



Scheme 4.7: Construction of C9 by Claisen rearrangement

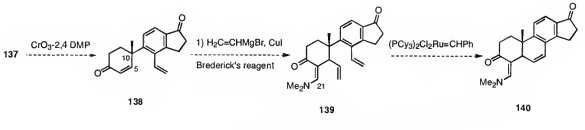
Reduction of commercially available 3-methylcyclohexenone **130** under Luche conditions gives allylic alcohol **131** in greater than 90% yield. Mitsunobu coupling[72] of this alcohol with phenol produces the aryl ether **133.** Under thermal and basic conditions the Claisen rearrangement[73] occurs to give phenol **134**. Under ennantioselctive CBS reduction conditions, the stereochemical information from **132** can be transferred to the quaternary center at the C9 position. Attempts to functionalize **132** are still being pursued in the lab.

Utilizing the Claisen based route would allow us to establish the methodology we would ultimately use to make analogs in the C1-deoxy viridin.



Scheme 4.8: Claisen approach to deoxy viridin

We already developed the basic chemistry that would be used for this synthesis in scheme 4.7 and would begin with a Mitsunobu coupling between the commercially available hydroxyindanone **110** and allyl alcohol **132** to give ether **135**. Heating of this compound under basic conditions should promote a rearrangement to yield phenol **136** with the difficult C10 center in place. The phenol function on **136** also provides a handle to form the C7-C8 bond via Stille coupling with a vinyl stannane to yield diene **137** (Scheme 4.8).

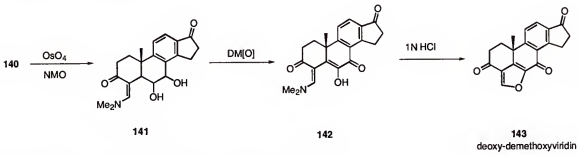


Scheme 4.9: Metathesis closure of ring-B

In this proposed route, the use of a ring-closing metathesis reaction to form the central B-ring by closure (Scheme 4.9). Installation of a vinyl group at C5 is facilitated by allylic oxidation[74] of **137** to ketone **138**. Conjugate addition of vinyl cuprate would be followed by trapping of the resulting enolate with Bredereck's reagent to produce **139**. Exposure of **139** to the Grubbs' ruthenium catalyst should affect direct closure of the B-ring, leaving convenient functionality in the form of an olefin, for introduction of the C6-

C7 vicinal dioxygenation. Compound **140** contains all the carbons of the required analog and could be prepared in as few as 8 steps from 3-methylcyclohexenone.

Completion of the analog synthesis would only require a few additional steps (Scheme 4.10). Introduction of the oxygen functionality on the B-ring will be accomplished in two steps. An initial osmylation should give the diol **141**, which upon further oxidation gives the enolic α-dione **142**. Closure to the furan would yield deoxy-demethoxviridin **143**.



Scheme 4.10: Deoxy-demethoxyviridin synthesis

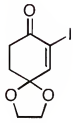
Conclusion

Two routes towards the synthesis of viridin and viridin analogs have been investigated. A Suzuki coupling and Claisen rearrangement were utilized in order construct the formation of the important C9-C10 bond. A route toward the closure of the B-ring is proposed and subsequent closure of the furan ring is envisioned. Further work in this area is currently under way.

Experimental Section

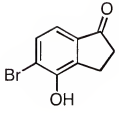
General methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury2000 at 300MHz and 75MHz respectively. Chemical shift (δ) are given in parts per million (ppm) and coupling constants (J), in hertz using TMS as an internal standard. The solvent was deuteriochloroform or deuteriobenzene where indicated. IR spectra were obtained as thin films between NaCl plates on a Perkin-Elmer 1600 series FTIR. The University of Florida Mass Spectroscopy Services performed all high-resolution mass spectra. All commercial materials were used without purification unless otherwise noted. The following solvents were distilled under positive pressure of dry argon: tetrahydrofuran (THF), diethyl ether (Et_2O) from sodium-benzophenone ketyl, methylene chloride (CH_2Cl_2) and toluene (C_6H_5-CH_3) from CaH_2. All the reactions were performed under an inert (Ar) atmosphere. Analytical thin-layer chromatography was performed using E. Merck silica 60-F254 coated 0.25-mm plates. Compounds were visualized by dipping the plates in an ammonium molybdate solution, iron chloride or potassium permanganate followed by heating. Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40-63 μm or 10-40 μm).

7-iodo-1,4-dioxa-spiro[4.5]dec-6-en-8-one



[104] To a flame dried 500 mL round bottom flask equipped with a stir bar under an atmosphere of argon was added **103** (500 mg, 3.2 mmol) and a solution of 10 mL CCl_4:pyridine (1:1) was added to the flask. The flask was cooled to 0°C in an ice water bath. To a 50 mL flame dried pear shaped flask under argon was added I_2 (3.5 g, 13.6 mmol) and 10 mL of a CCl_4:pyridine (1:1) solution. The I_2 was allowed to dissolve and the solution in the pear shaped flask was added drop wise to the round bottom flask via syringe. After addition was complete, the reaction flask was allowed to warm to room temperature and left to stir for 12 hours. The reaction mixture was diluted with 100 mL diethyl ether. The organic layer was washed with 20% $Na_2S_2O_3$ (3 x 25 mL), followed by1M HCl (3 x 25 ml, ice added to the separatory funnel), and brine (1 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield dark brown oil. The crude residue was purified by flash chromatography (Hex:EtOAc 75:25) to yield a light yellow oil (826 mg, 91%). IR (KBr plate) 1692, 1021, and 1116 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (t, 2H), 2.80 (t, 2H), 4.00 (m, 4H), 7.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.3, 33.5, 65.3, 105.3, 107.5, 155.4, and 191.6; HRMS (EI) m/z (M^+) calcd. for $C_8H_9O_3I$, 279.9596, found 279.9582.

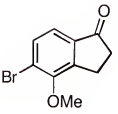
5-Bromo-4-hydroxy-indan-1-one



[111a] To a flame dried flask equipped with a stir bar under an atmosphere of argon was added 13.5 mL CH_2Cl_2. The flask was cooled to -78 °C and *t*-butylamine (1.42 mL, 13.5 mmol) was added to the flask via syringe followed by drop wise addition of Br_2 (0.35 mL, 6.75 mmol) with stirring. A yellow/orange precipitate formed during addition and the reaction flask was left to stir at -78 °C. The solution turned creamy white at which time the flask was slowly warmed to room temperature. The mixture was stirred at room temperature for 90 min before another 13.5 mL of CH_2Cl_2 was added to the rxn flask. The rxn flask was cooled again to -78 °C and an additional 13.5 mL of CH_2Cl_2 was added (40.5 mL CH_2Cl_2 total in flask). The solution was cooled to -78 °C and **110** (1.00g, 6.75 mmol) was quickly added to the stirring mixture. The reaction was allowed to stir at for 30 minutes. The reaction was quenched with 29 mL of a saturated water:MeOH solution of $Na_2S_2O_3$. The resulting mixture was warmed to room temperature and all solvents were removed under reduced pressure to yield a light brown residue. The residue was purified by flash chromatography (CH_2Cl_2 eluent), yielding an off white solid (0.842 g, 55%). IR (KBr plate) 3350, 1706, 1219, and 1156 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (t, 2H, J = 5.6 Hz), 3.10 (t, 2H, J = 5.6 Hz), 5.82 (d, 1H, J = 8.2 Hz), 7.22 (d, 1H, J = 8.2 Hz), 7.48 (d, 1H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 36.5, 116.6, 131.8; HRMS (EI) m/z (M^+) calcd. for $C_9H_7O_2Br$ 225.9629, found 225.9627.

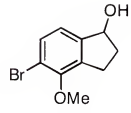
Anal. calcd. for $C_9H_7O_2Br$: C, 47.61; H, 3.11. Found: C, 47.21; H, 2.95

5-Bromo-4-methoxy-indan-1-one



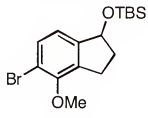
[111b] To a flame dried 100 mL round bottom flask equipped with a condenser was added **111a** (0.258 g, 1.14 mmol) and 5 mL reagent grade acetone. Dimethylsulfate (0.2 mL, 1.7 mmol) and solid K_2CO_3 (0.236 g, 1.7 mmol) were then added. The reaction mixture was refluxed for 2 hr and then quenched with 5 mL water. The resulting mixture was extracted with diethyl ether (3 x 15 mL). The ether layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a yellow oil (0.248 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70 (t, 2H, J = 6.0 Hz), 3.20 (t, 2H, J = 6.0 Hz), 3.85 (d, 3H, J = 3.7 Hz), 7.36-7.42 (d, 1H, J = 7.9 Hz), 7.56-7.62 (d, 1H, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 37.0, 54.4, 55.9, 115.9, 133.3, 146.9, 156.5, 176.8, and 208.8; HRMS (EI) m/z (M^+) calcd. for $C_{10}H_9O_2Br$ 239.9786, found 239.9710.

5-Bromo-4-methoxy-indan-1-ol



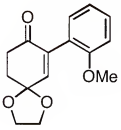
[147] To a 25 mL round bottom flask equipped with a stir bar was added **111** (1.1 g, 4.56 mmol) and 2 mL MeOH. The flask was cooled to 0°C in an ice-water bath. $NaBH_4$ was added in portions with stirring. The flask was allowed to warm to room temperature and the reaction mixture was stirred for an additional 30 minutes before being quenched with 2 mL water. The resulting mixture was extracted with diethyl ether (3 x 20 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a white semi-solid (1.02 g, 92%). IR (KBr plate) 3275, 1276, and 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (d, 1H, J = 0.02 Hz), 1.90-2.04 (m, 1H), 2.44-2.56 (m, 1H), 2.82-2.94 (m, 1H), 3.08-3.20 (m, 1H), 3.85 (s, 3H), 5.20 (q, 1H, J = 0.04 and 0.02 Hz), 7.01-7.06 (d, 1H, J = 0.03 Hz), 7.41-7.45 (d, 1H, J = 0.03 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 27.6, 36.2, 60.4, 76.3, 116.3, 121.1, 132.5, 136.9, 147.2, and 153.5; HRMS (EI) m/z (M^+) calcd. for $C_{10}H_{11}O_2Br$ 241.9942, found 241.9941.

(5-Bromo-4-methoxy-indan-1-yloxy)-*tert*-butyl-dimethyl-silane



[112] To a 50 mL round bottom flask equipped with a stir bar under an atmosphere of argon was added 10 mL CH_2Cl_2, **147** (0.520 g, 2.14 mmol), imidazole (0.219 g, 3.21 mmol), and TBSCl (0.484 g, 3.21 mmol). The reaction mixture was stirred at room temperature for 12 hours before being quenched with 5 mL saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to yield a light yellow oil (0.688 g, 90%). IR (KBr plate) 1276, 1260, and 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88-2.02 (m, 1H), 2.38-2.52 (m, 1H), 2.74-2.88 (m, 1H), 3.04-3.16 (m, 1H), 5.16-5.28 (t, 1H, J = 0.02 Hz), 6.90-7.00 (d, 1H, J = 0.03 Hz), 7.36-7.46 (d, 1H, J = 0.03 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.4, -4.2, 18.4, 26.1, 27.4, 36.7, 60.3, 76.4, 115.4, 120.9, 132.1, 136.1, 147.9, 153.3.

7-(2-methoxy-phenyl)-1,4-dioxa-spiro[4.5]dec-6-en-8-one



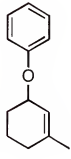
[107] To a flame dried 25 mL round bottom flask equipped with a stir bar, a Dean-Stark trap and condenser was added 4 mL benzene, **104** (0.200 g, 0.71 mmol), **151** (0.120 g, 0.79 mmol), Ag_2CO_3 (0.218 g, 0.79 mmol), and $Pd(PPh_3)_4$ (0.050 g, 0.043 mmol). The reaction mixture was refluxed for 72 hours. The black solution was quenched with 1 mL 2N HCl and the dark residue was filtered through a bed of celite and rinsed 3x with 2N HCl. The filtrate was diluted with CH_2Cl_2 (20 mL) and the organic layer was washed with water (1 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to yield a crude clear brown residue. The crude product was purified by flash chromatography (Hex:EtOAc 75:25) to yield a pale yellow oil (0.149 g, 80%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (m, 2H), 2.80 (m, 2H), 3.80 (s, 3H), 4.10 (s, 4H), 6.60 (s, 1H), 6.80-7.00 (m, 2H), 7.10 (dd, 1H, J = 1.9 and 1.9 Hz), 7.20-7.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.0, 35.6, 36.2, 55.8, 65.2, 104.8, 111.1, 120.6, 125.3, 129.9, 130.5, 140.1, 143.3, 157.2, and 196.9; HRMS (EI) m/z (M^+) calcd. for $C_{15}H_{16}O_4$ 260.1049, found 260.1047.

Anal. calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20 Found: C, 69.41; H, 6.12

3-methylcyclohexenol

[131] To a 50 mL round bottom flask equipped with a stir bar was charged with **130** (1.00 g, 9.08 mmol), 23 mL MeOH and $CeCl_3 \cdot 7H_2O$ (5.07 g, 13.5 mmol). The flask was cooled to 0°C in an ice-water bath and solid $NaBH_4$ (0.515 g, 13.6 mmol) was added to the reaction flask portion wise with stirring. The flask was warmed to room temperature and left to stir for 1 hour. The reaction was quenched with 3 mL saturated $NaHCO_3$ and the MeOH was removed under reduced pressure. The resulting mixture was diluted with 10 mL water and extracted with diethyl ether (3 x 30 mL). The organic layers were combined, washed with brine and dried over anhydrous $MgSO_4$. Diethyl ether was removed under vacuum to yield a pale yellow oil (0.956 g, 94%). IR (KBr plate) 3250 and 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-1.60 (m, 2H), 1.62-1.70 (s, 3H), 1.72-1.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.8, 30.2, 31.8, 66.0, 124.4, 138.8; HRMS (EI) m/z (M^+) calcd. for $C_7H_{12}O$ 112.0888, found 112.0885.

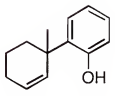
(3-methyl-cyclohex-2-enyloxy)-benzene



[133] To a flame dried 250 mL round bottom flask equipped with a stir bar under an atmosphere of argon was charged with 100 mL THF and cooled to 0°C. To the flask, **131** (1.4g, 12.5 mmol), PPh_3 (4.91g, 18.7 mmol) and phenol (1.6g, 18.7 mL) were added. Diisopropyl azodicarboxylate (3.78g, 18.7 mmol) dissolved in ca. 5 mL of dry toluene was added drop wise over 20 minutes with stirring. The reaction mixture was left to stir for 24 hours. Once all of **131** were consumed (monitored by TLC), 30 mL of hexanes was added and the white precipitate formed was filtered. The filtrate was concentrated under vacuum and the crude residue purified by flash chromatography (Hex:EtOAc 85:15) to yield a colorless oil (2.1 g, 87%). IR (KBr plate) 1244, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-1.70 (m, 2H), 1.69 (s, 3H), 1.80-2.00 (m, 4H), 4.75 (s, 1H), 5.61 (s, 1H), 6.87-6.91 (m, 2H), 7.19-7.30 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.8, 28.0, 30.2, 71.2, 115.8, 120.5, 123.1, 128.5, 129.5, 133.6, 140.2, and 157.9; HRMS (EI) m/z (M^+) calcd. for $C_{13}H_{16}O$ 188.1201, found 188.1204;

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.46; H, 8.24.

2-(1-Methyl-cyclohex-2-envl)-phenol

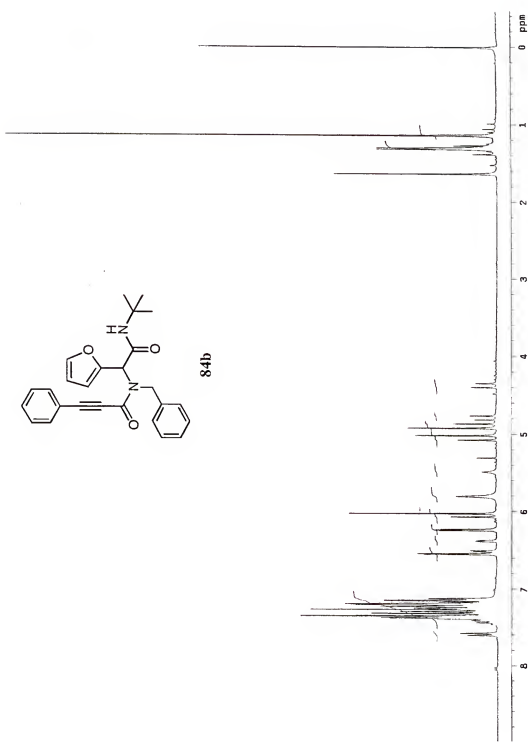


[134] A base washed, silylated glass tube was charged with **133** (1.0g, 5.3 mmol) and 10 mL of N,N-dimethylaniline. The tube was sealed tightly and immersed in a pre-heated sand bath at 200°C for 24 hours. The glass tube was cooled to room temperature and the grey solution was transferred to a separatory funnel containing ice and 2 mL concentrated HCl. Water was added to the funnel (15 mL) and organic layer was extracted (2 x 15 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum to yield a yellow-brown residue. The residue was purified by chromatography (Hex:EtOAc 95:5) to yield a pale yellow oil (0.71 g, 72%). IR (KBr plate) 3487, 1269, 1273 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 1.81 (m, 2H), 1.94 (m, 4H), 5.19 (s, 1H), 6.05 (bs, 1H), 6.95 (m, 2H), 7.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 28.1, 31.4, 36.2, 49.1, 111.3, 115.3, 122.2, 127.6, 129.3, 131.1, 144.2, 157.8, HRMS (EI) m/z (M^+) calcd. for $C_{13}H_{16}O$ 188.1201, found 188.1211.

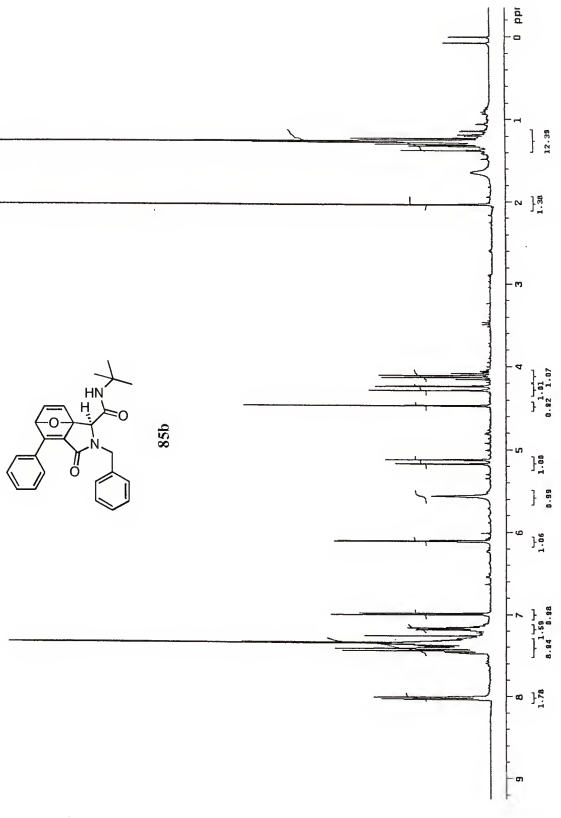
Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.66; H, 8.49.

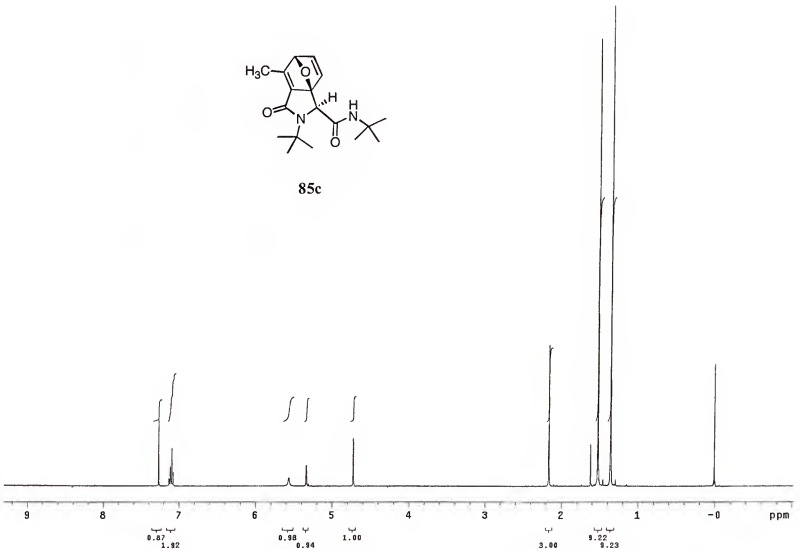
APPENDIX A
NMR (^{1}H & ^{13}C) SPECTRA OF SELECTED COMPOUNDS

84a
ppm
8.95
2.16
1.02
2.17
1.01
2.03
3.08
4.03

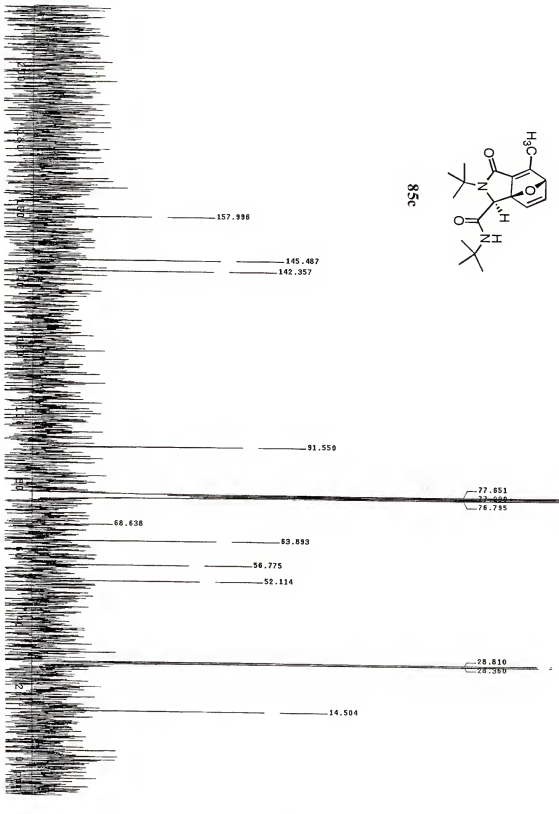


84b

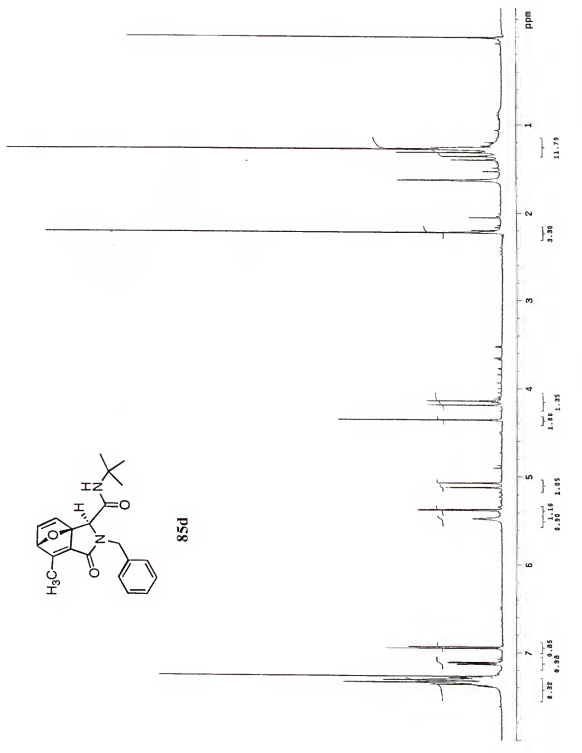

HN
H
O
O
O
N
85b
ppm
0
1
2
3
4
5
6
7
8
9
12.39
1.38
0.92, 1.07
1.00
0.99
1.06
1.58
8.84, 8.88
1.78



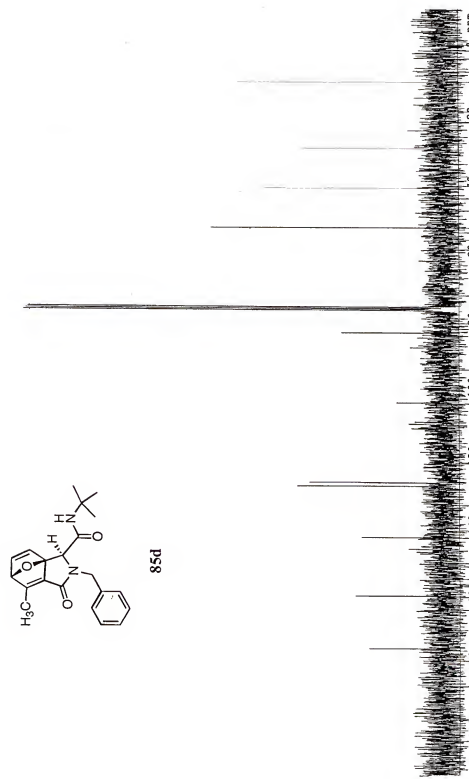
85c


157.996
145.487
142.357
91.550
77.651
76.795
68.638
63.893
56.775
52.114
28.810
28.380
14.504

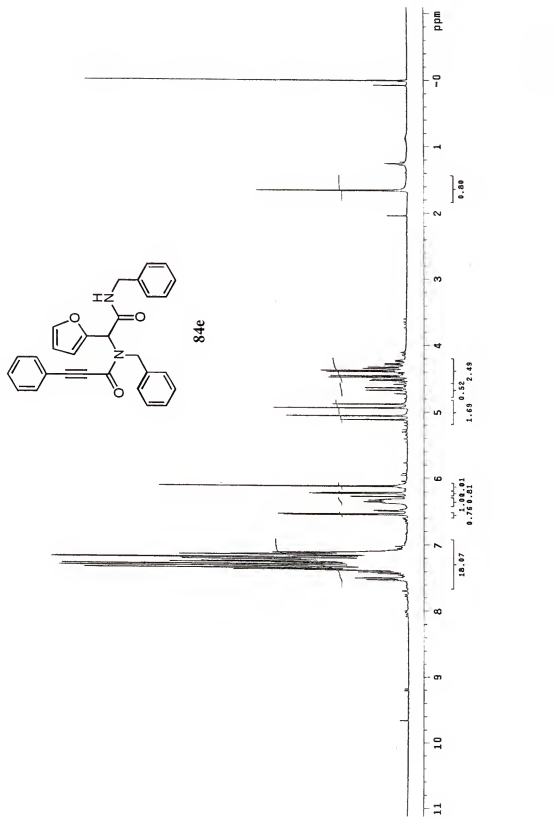
85c

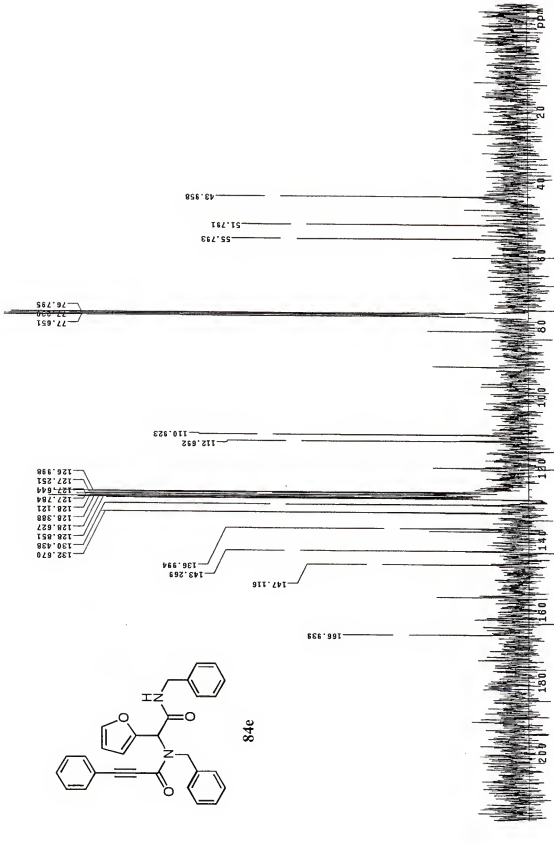


85d

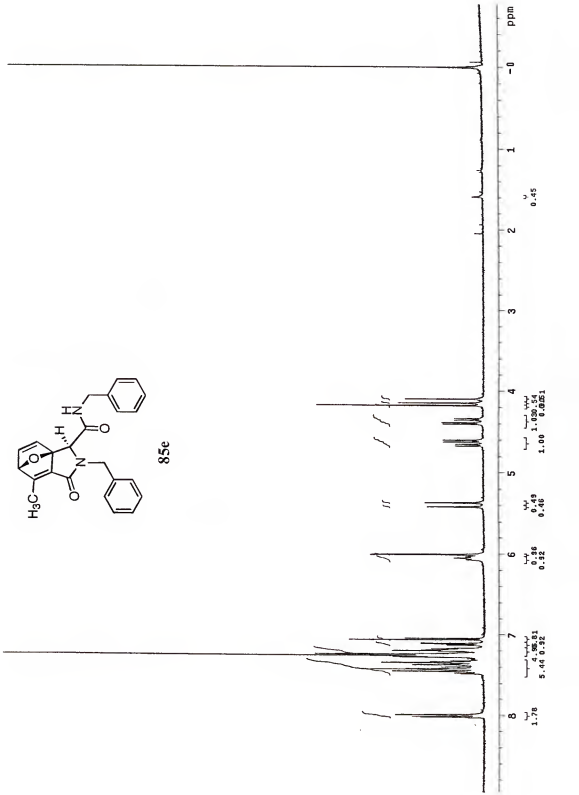


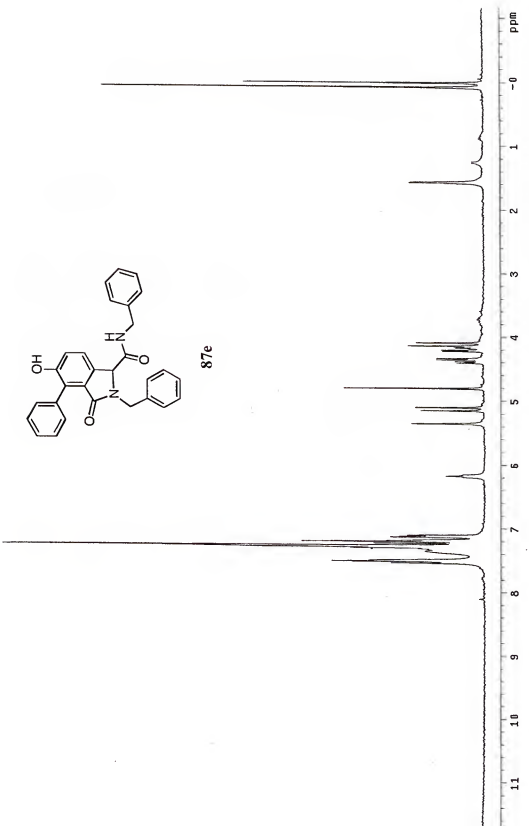
85d

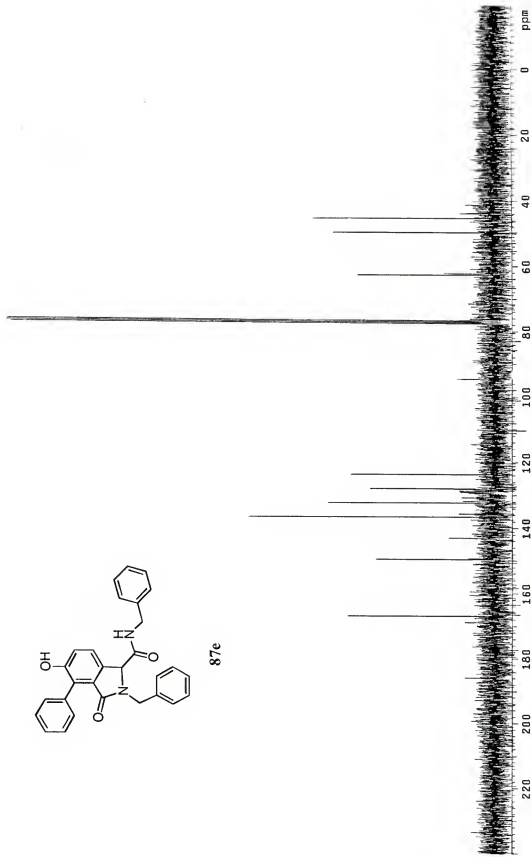

84e
ppm
19.97
1.69
0.52
2.49
0.99


166.333
147.116
143.269
136.994
132.670
130.436
126.851
126.588
126.527
126.121
127.644
127.284
127.251
126.986
112.692
110.923
77.651
77.000
76.795
55.793
51.791
49.958
200
180
160
140
120
100
80
60
40
20
0

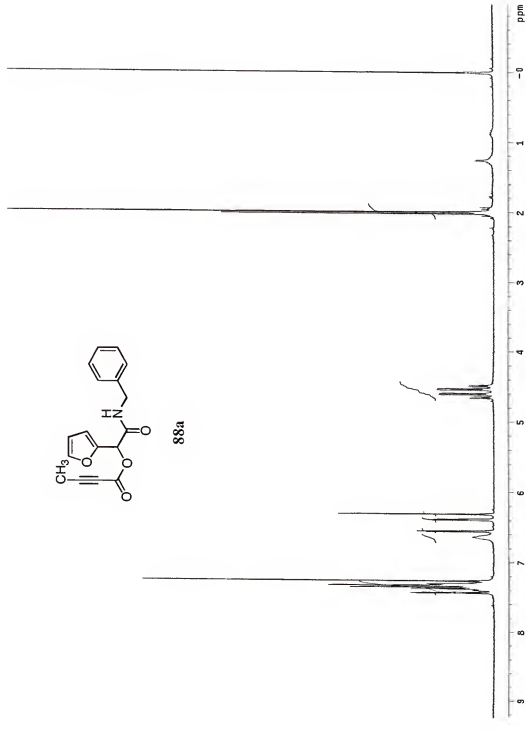
84e

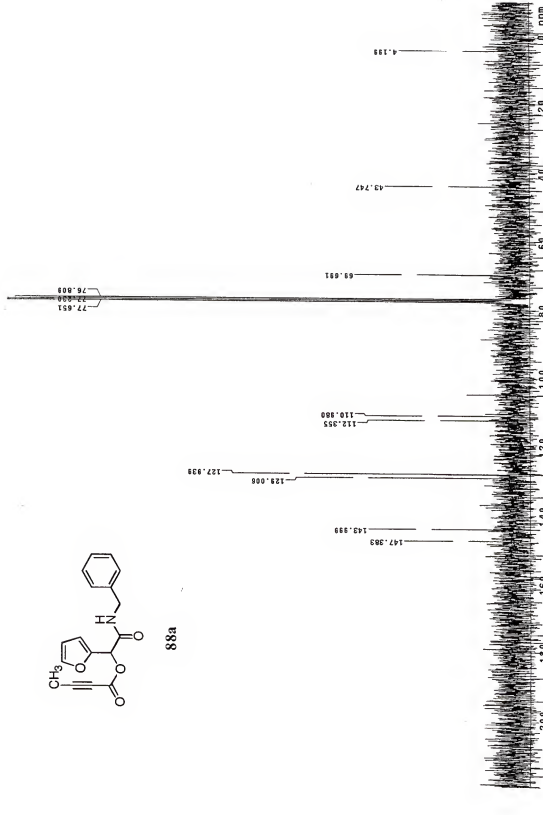

H3C
O
H
N
O
N
O
85e
ppm

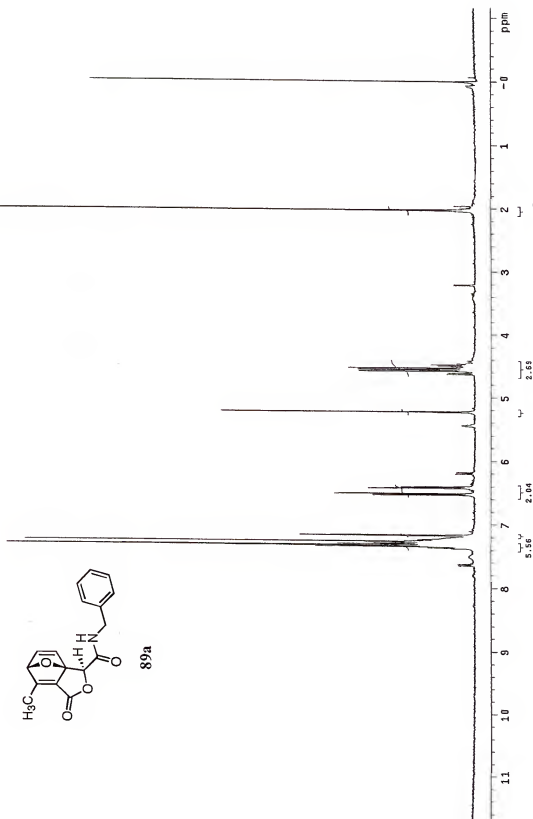

OH
O
N
H
N
O
O
87e
ppm
11
10
9
8
7
6
5
4
3
2
1
0

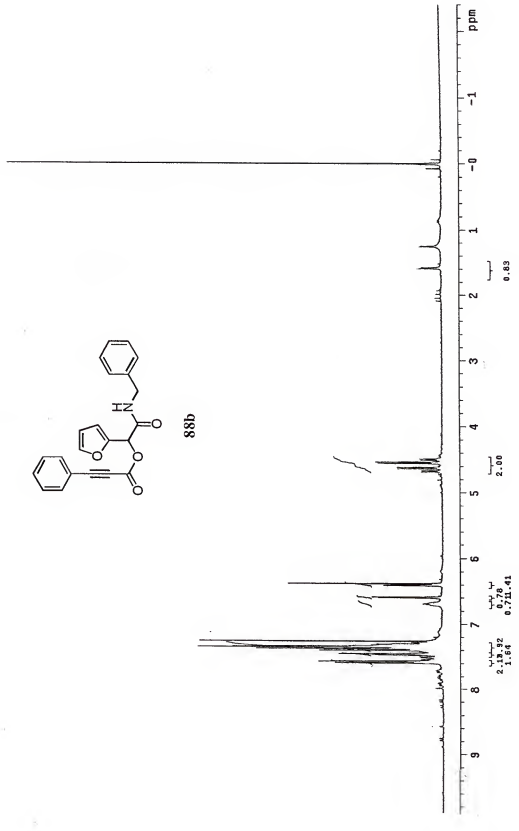


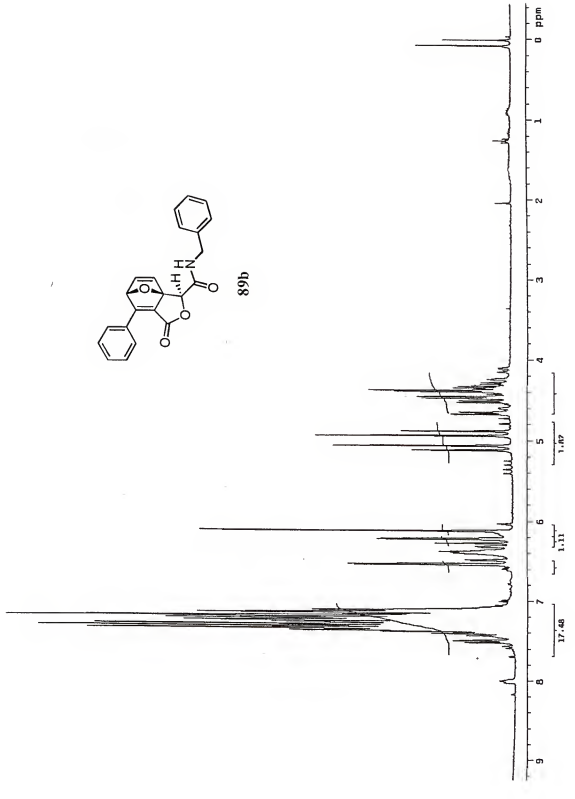
87e

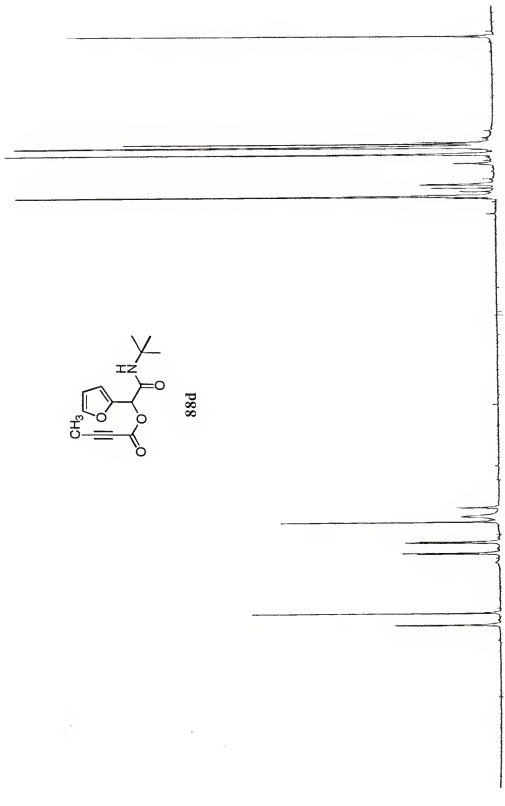

88a
ppm


147.383
143.999
129.006
127.939
112.355
110.860
77.651
77.330
76.809
69.651
43.747
4.199
ppm
88a

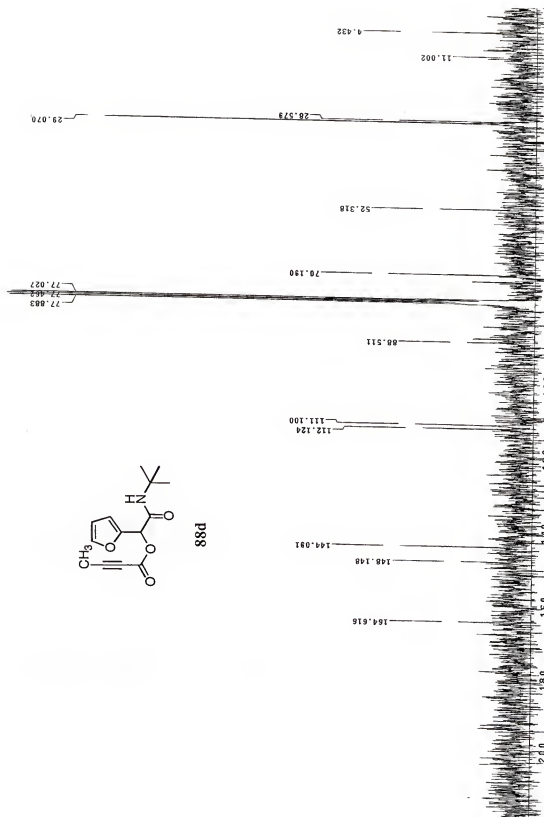

89a
ppm
5.56
1.20
2.04
1.00
2.69
3.15


88b
ppm
2.13,32
1.64
0.78
0.71
1.41
2.00
0.83

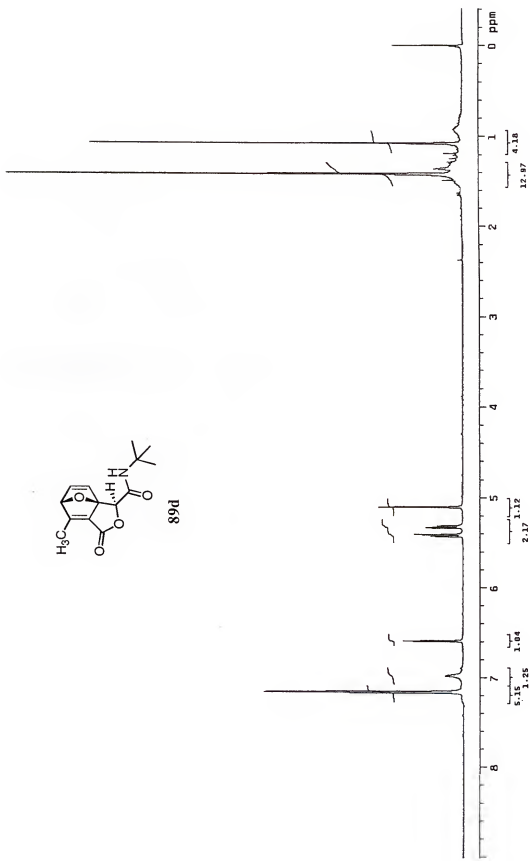

89b
ppm
17.48
1.11
1.69

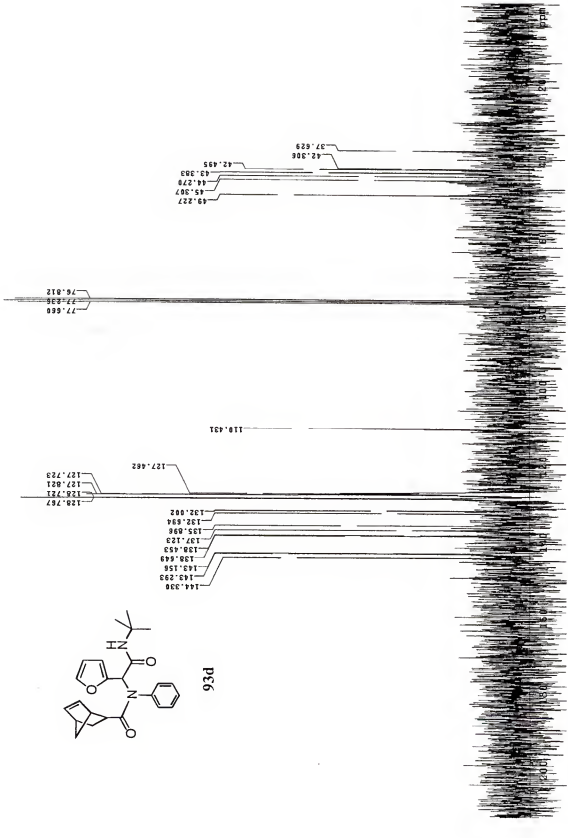


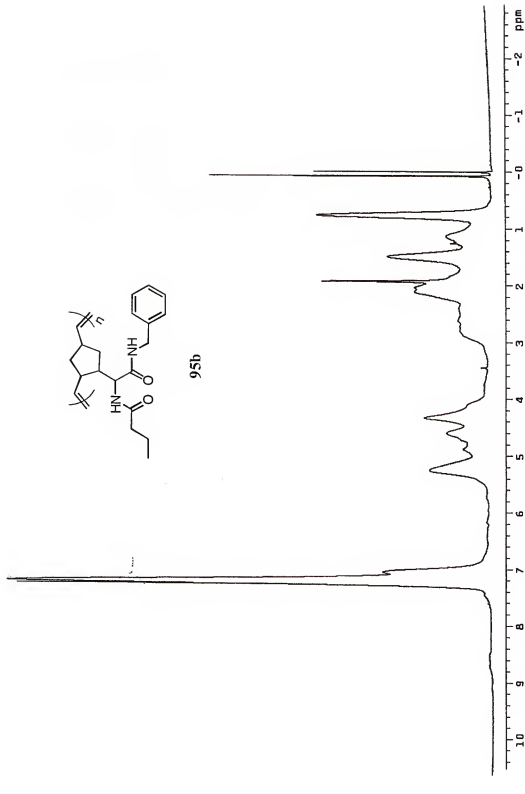
88d

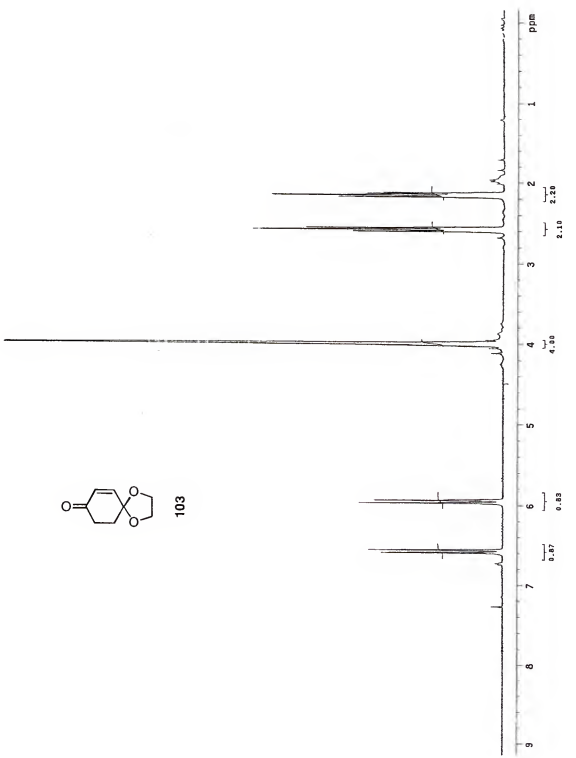

4.432
11.002
28.579
29.070
52.318
70.180
77.027
77.883
88.511
111.100
112.124
144.081
148.148
164.616
20
40
60
80
100
120
140
160
180
200
220
O
O
O
H
N
CH3

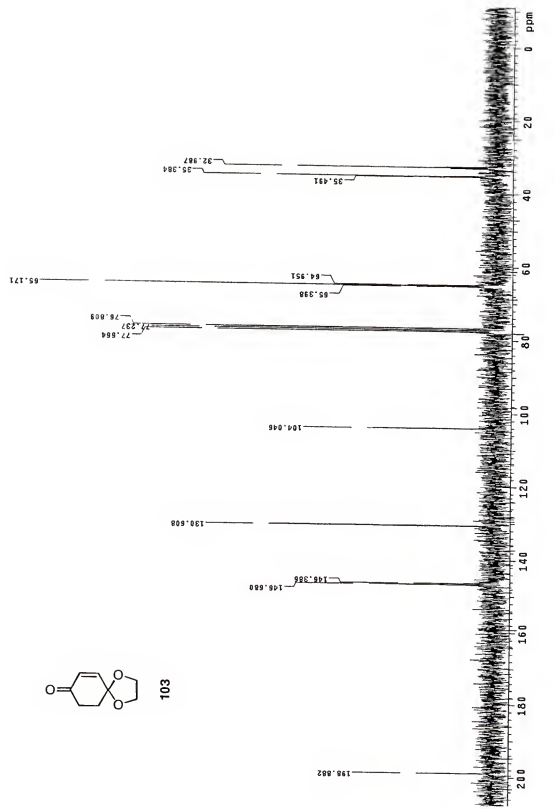
88d


H3C
O
O
O
H
N
O
p68
ppm
0
1
2
3
4
5
6
7
8
12.97
4.18
2.17
1.12
5.15
1.25
1.04

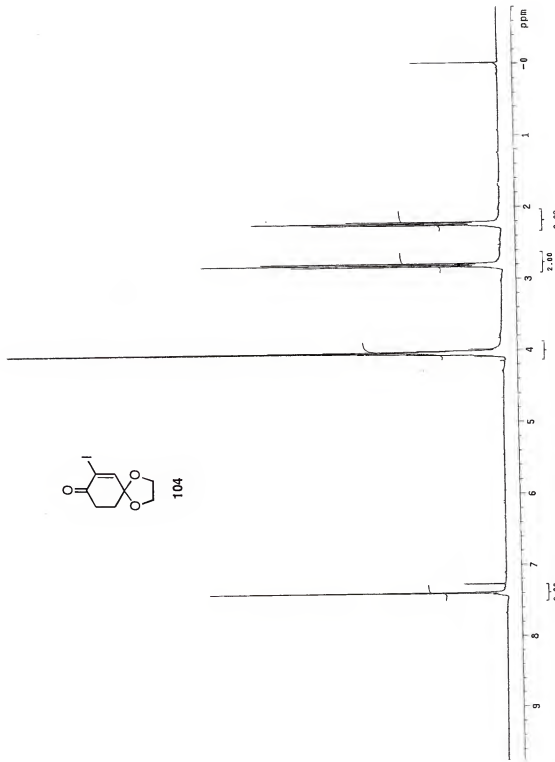

p26
144.330
143.293
143.156
138.449
137.123
135.696
132.694
132.402
129.767
128.721
127.021
127.729
127.462
119.431
77.660
77.336
76.812
69.227
65.367
64.279
63.383
62.495
62.306
37.629

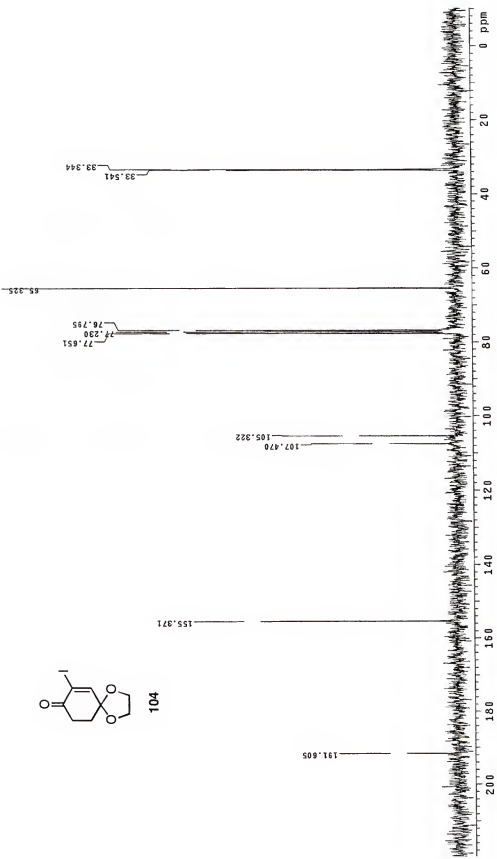

95b
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

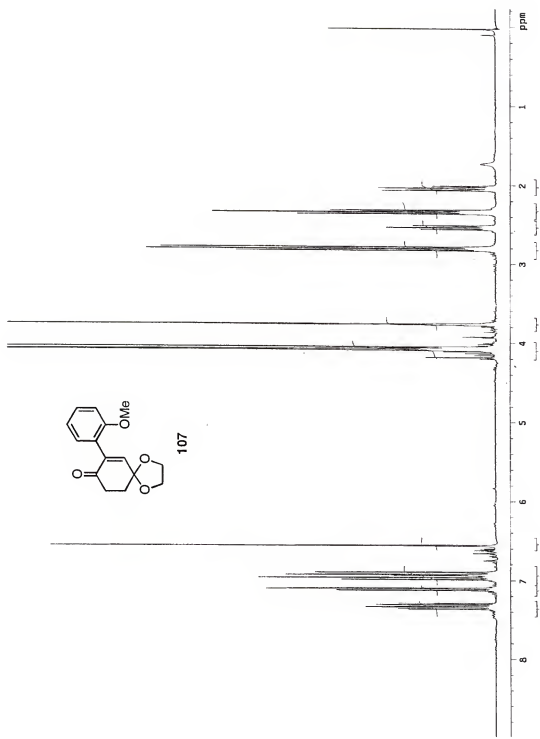

103
ppm
2.20
2.10
4.00
0.83
0.97

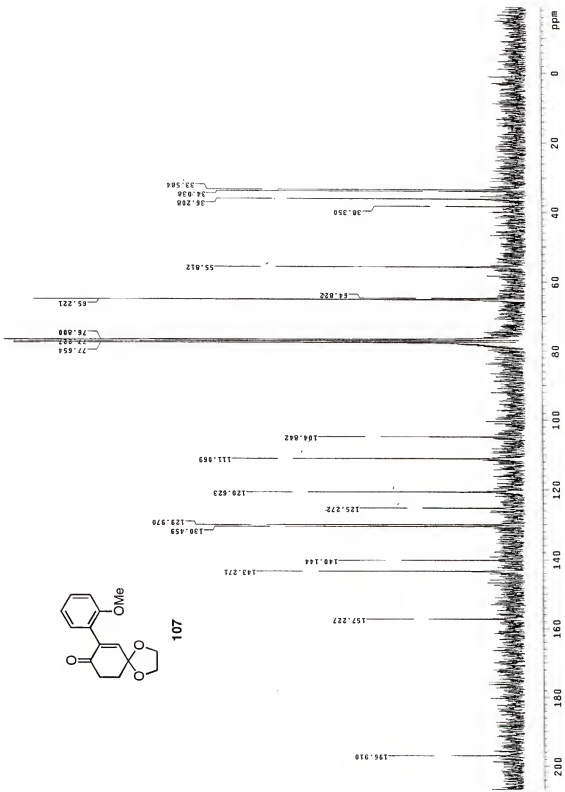

198.682
146.660
146.388
130.608
104.046
77.884
77.237
76.809
65.388
64.951
65.171
35.491
35.384
32.987
0 ppm
20
40
60
80
100
120
140
160
180
200

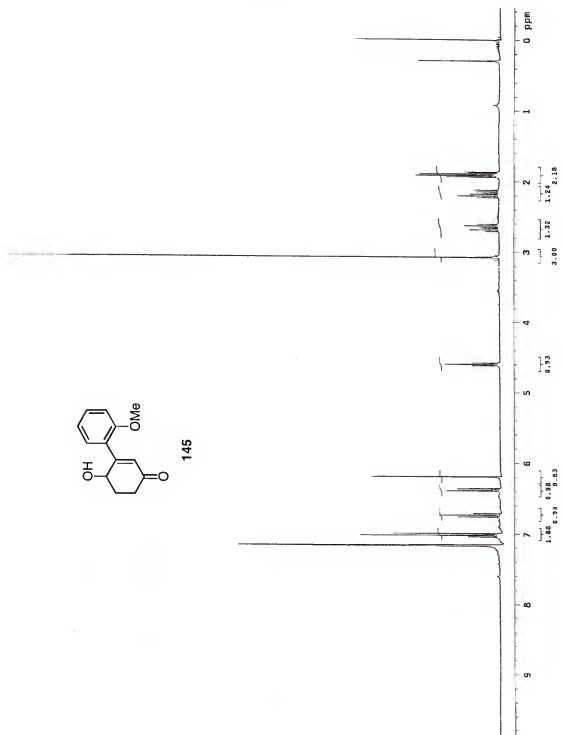
103

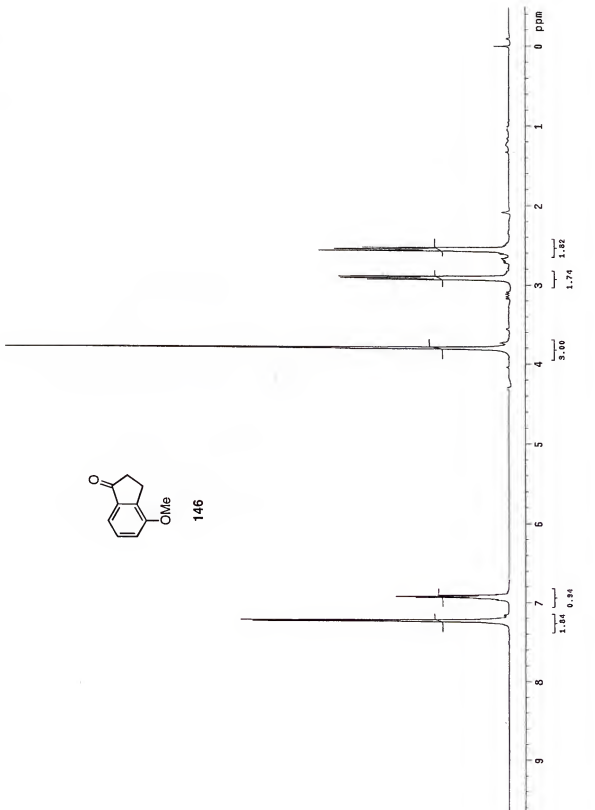

104
ppm
0
1
2
3
4
5
6
7
8
9
2.69
2.00
3.35
0.86

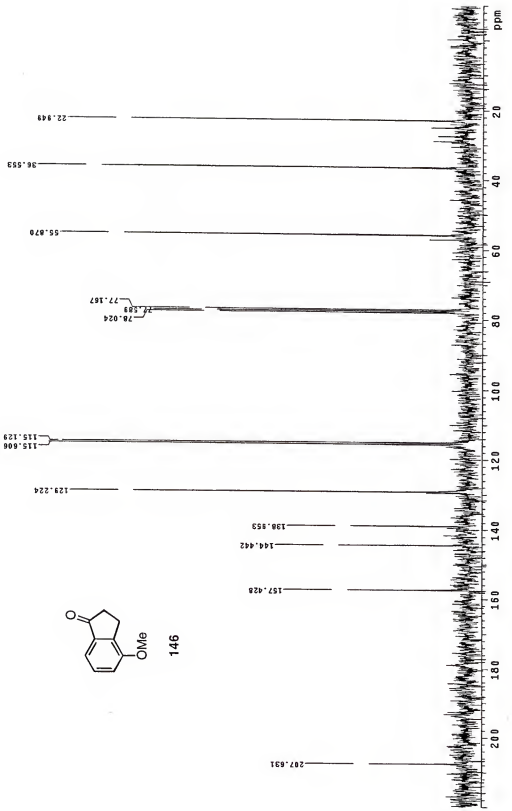

191.605
155.371
107.470
105.322
77.651
77.230
76.795
65.325
33.541
33.344
ppm
104

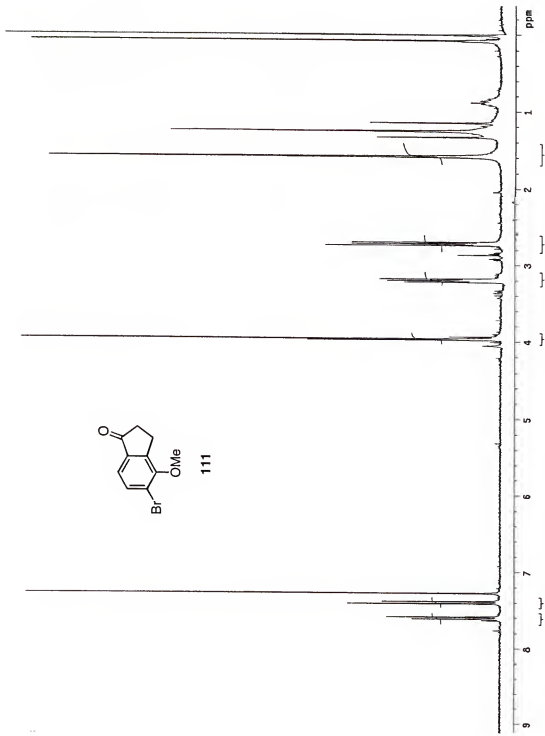

OMe
O
O
O
107
ppm
1
2
3
4
5
6
7
8
1.00
2.04
0.86
5.24
3.10
1.46
6.83
3.96
0.91

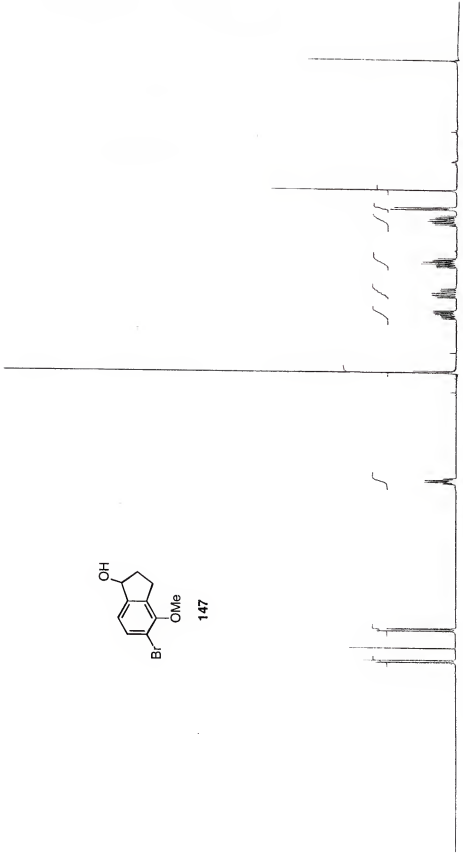

OMe
O
O
O
107
196.910
157.227
143.271
140.144
130.459
129.970
125.272
120.623
111.069
106.642
77.654
77.037
76.600
65.221
64.822
55.612
36.288
34.034
33.564
30.350
ppm
0
20
40
60
80
100
120
140
160
180
200

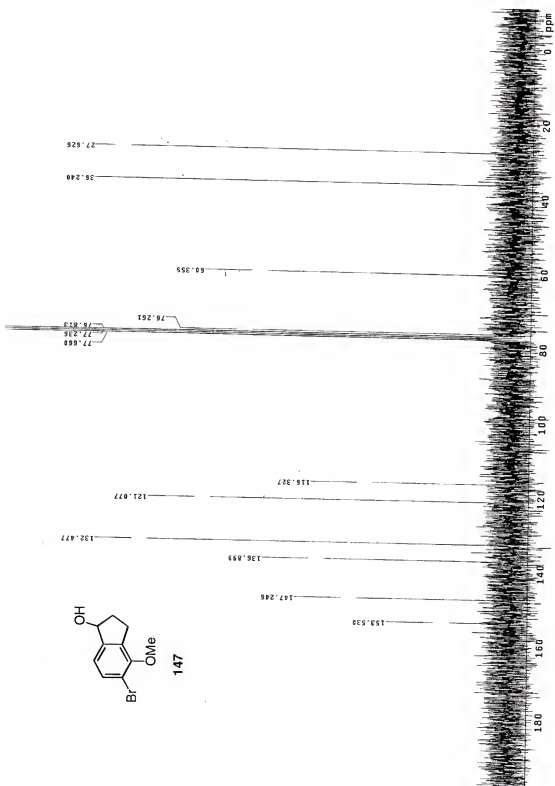

OMe
OH
O
145
ppm

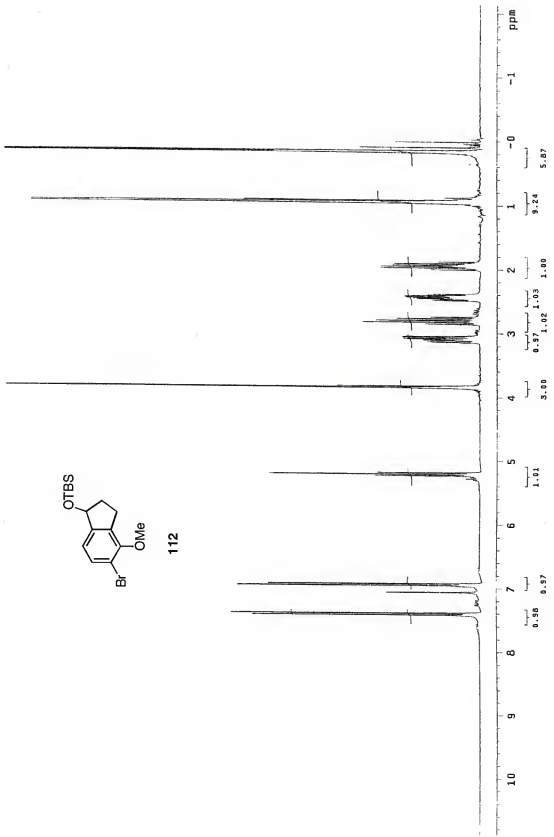

O
OMe
146
ppm
0
1
2
3
4
5
6
7
8
9
3.00
1.74
1.82
1.84
0.94

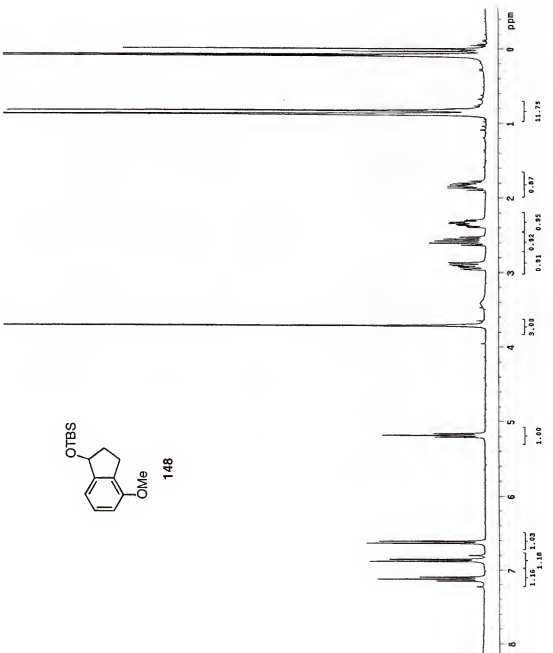

207.631
157.428
144.462
138.353
129.224
115.606
115.129
78.024
77.189
77.167
55.670
36.553
22.949
ppm
20
40
60
80
100
120
140
160
180
200
OMe
146

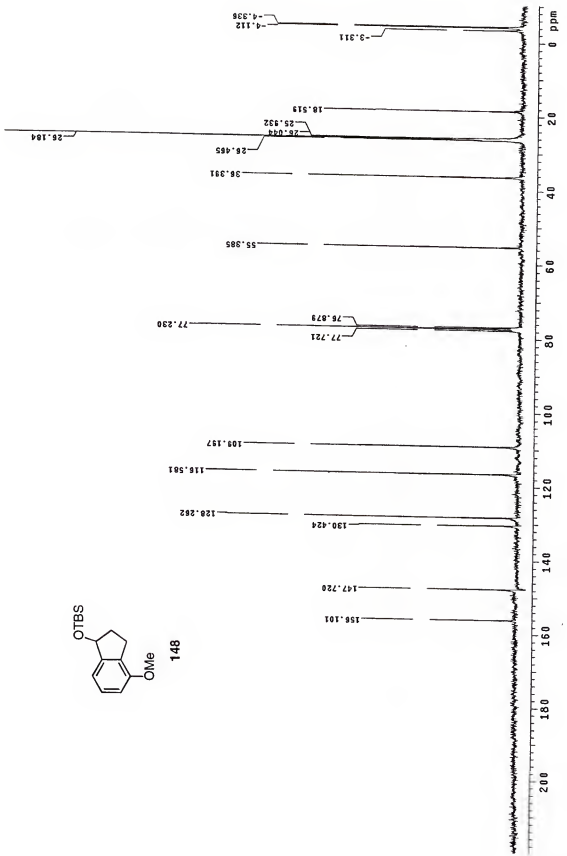

O
OMe
Br
111
ppm
1
2
3
4
5
6
7
8
9
3.89
1.70
1.67
1.60
0.97
0.88

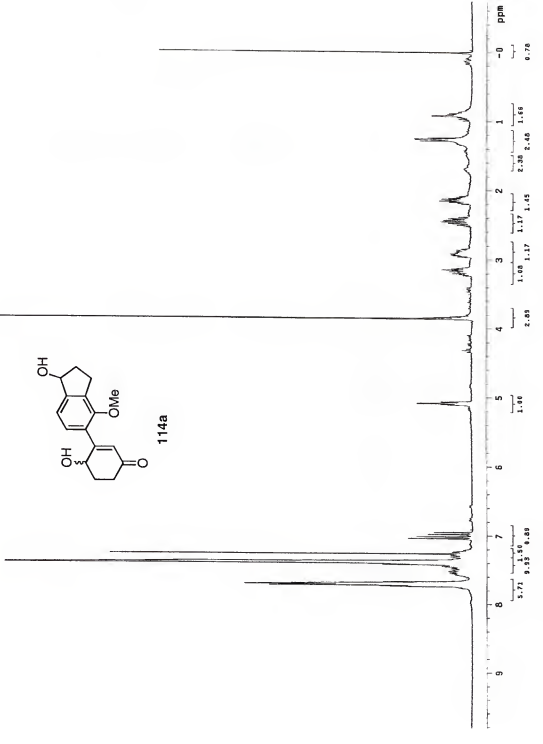

OH
OMe
Br
147
ppm
0
1
2
3
4
5
6
7
8
9
0.95
1.01
1.62
0.87
1.01
1.75
3.00
0.99
0.97
0.35

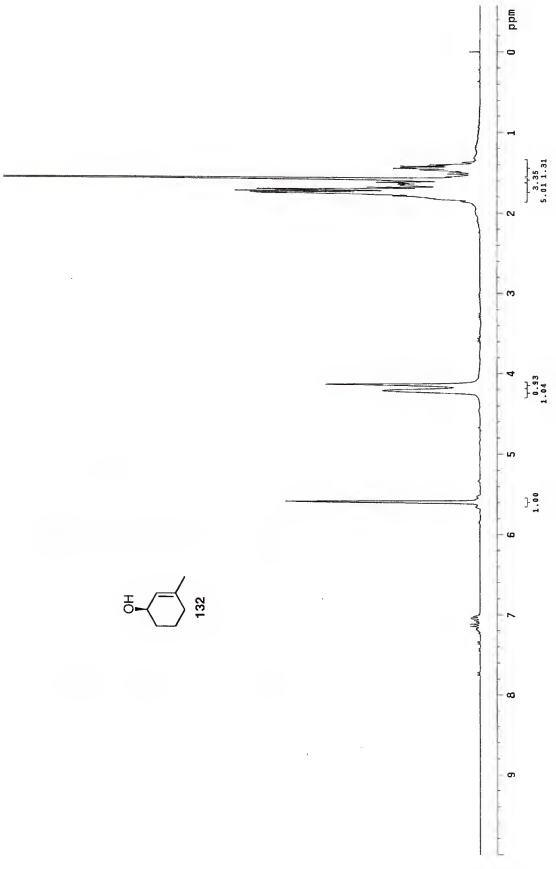

153.538
147.246
136.699
132.477
123.077
116.327
77.668
77.236
76.813
76.261
60.355
36.240
27.626
ppm
0
20
40
60
80
100
120
140
160
180
OH
OMe
Br
147

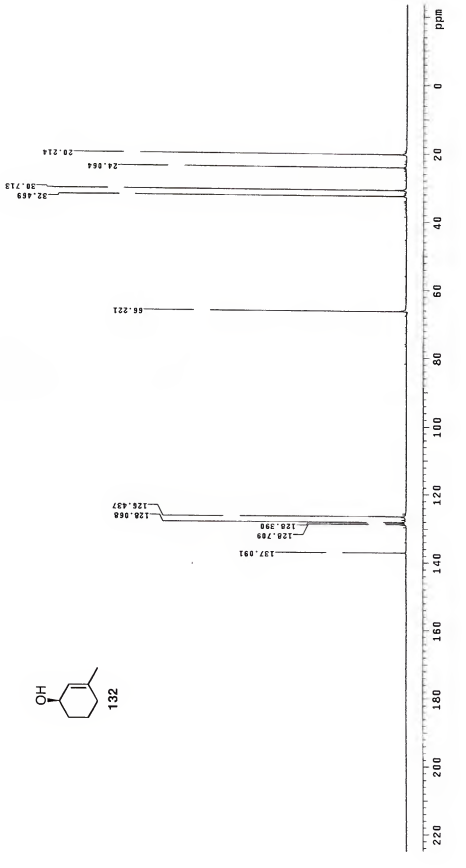

OTBS
OMe
Br
112
ppm

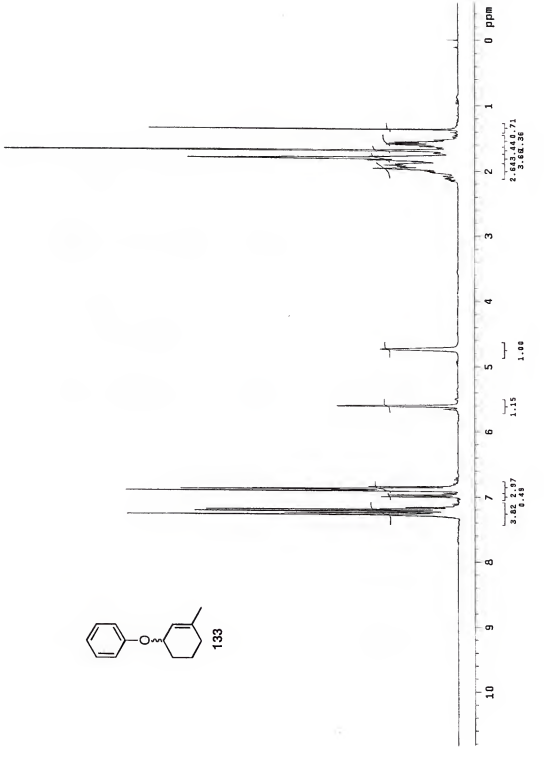

OTBS
OMe
148
ppm

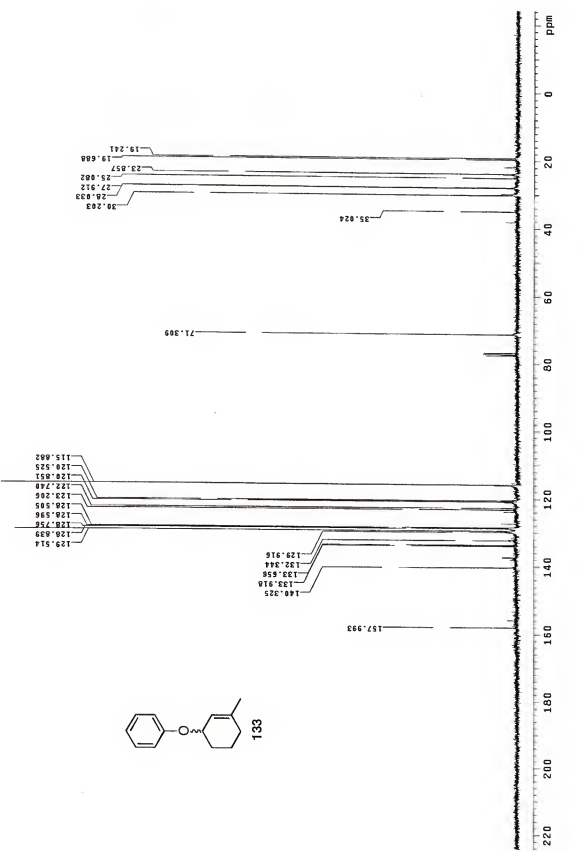

OTBS
OMe
148
158.101
147.720
130.424
128.282
116.561
109.197
77.721
76.879
77.230
55.385
38.391
26.464
25.044
25.332
26.164
18.519
-3.311
-4.112
-4.336
0
20
40
60
80
100
120
140
160
180
200
ppm

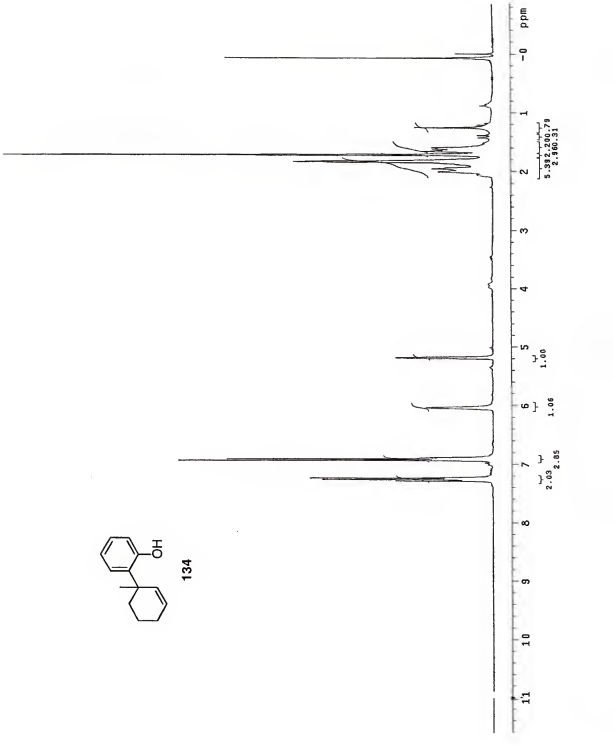

OH
OMe
OH
O
114a
ppm

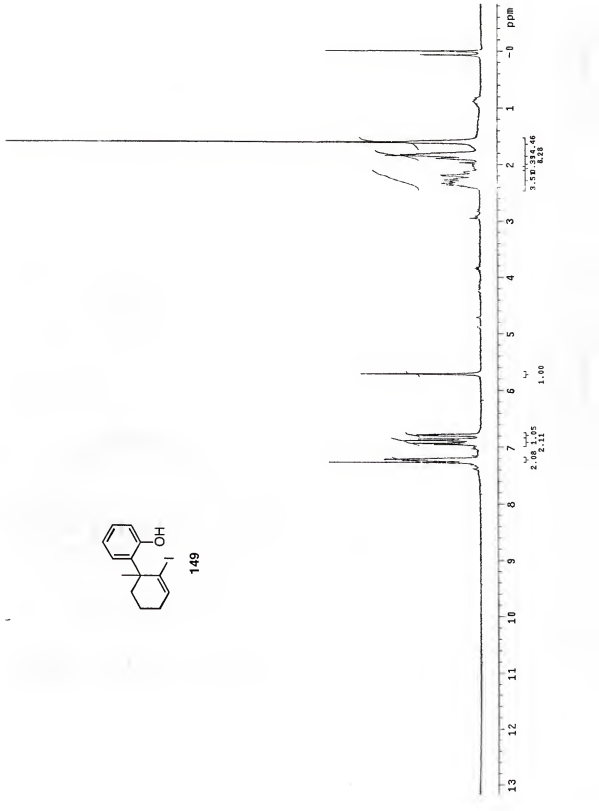

OH
132
ppm
0
1
2
3
4
5
6
7
8
9
1.00
0.93
1.94
3.35
5.01
1.31

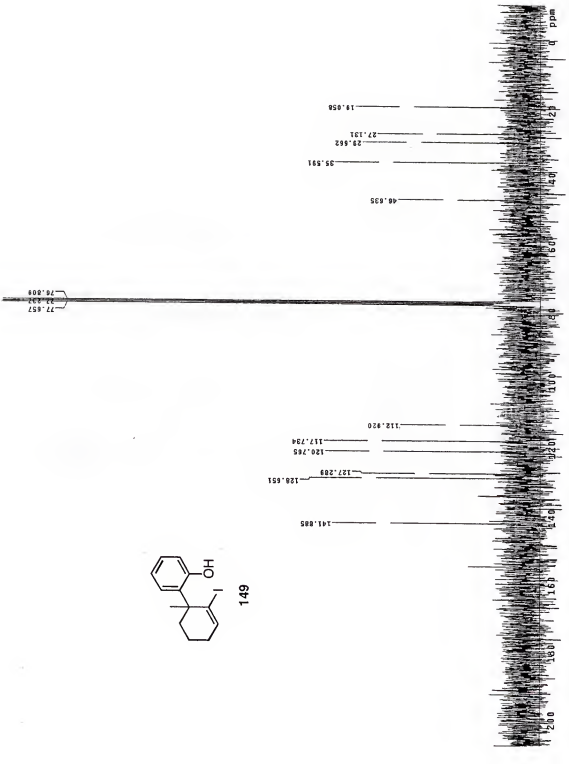

ppm
0
20
40
60
80
100
120
140
160
180
200
220
20.214
24.864
30.713
32.469
66.221
126.437
126.068
126.789
128.398
137.091
OH
132


133
ppm
0
1
2
3
4
5
6
7
8
9
10
2.643.44
0.71
3.66
0.36
1.15
1.00
3.82
2.97
0.49


157.993
148.325
133.918
133.656
132.344
129.916
129.514
128.699
128.756
128.596
128.505
123.206
122.748
120.851
120.525
115.882
71.369
35.024
30.203
26.033
25.902
27.912
23.857
19.688
19.241
ppm
0
20
40
60
80
100
120
140
160
180
200
220
133


OH
134
ppm
2.43
2.85
1.06
1.00
5.32
2.46


OH
I
149
ppm
2.08
1.05
2.11
1.00
3.51
384.46
4.00


141.885
137.209
128.651
120.765
117.734
112.820
77.657
76.809
46.635
39.591
29.662
27.151
19.058
ppm

OH

149

LIST OF REFERENCES

1. Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135-8173.

2. Wender, P. A.; Handy, S. T.; Wright, D. L. *Chemistry & Industry* **1997**, 765.

3. Trost, B. M. *Science* **1991**, *254*, 1471.

4. Ugi, I.; Johberger, S.; Karl, R. The Passerini and Ugi Reactions In Comprehensive Organic Synthesis, Trost, B.M., Fleming, I., Eds.; Pergamon: Oxford, **1991**, *2*, 1083.

5. Falck, J. R.; Manna, S. *Tetrahedron Lett.* **1981**, *22*, 619-620.

6. Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355-6366.

7. Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4068-4069.

8. Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *24*, 9310-9313.

9. Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293-8296.

10. Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729-2730.

11. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem.Res.* **1996**, *29*, 123-131.

12. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366-374.

13. Ugi, I.; Steinbrucker, *Chem. Ber.* **1961**, *94*, 734-42.

14. Ugi, I.; Domling, A.; Gruber, B.; Heilig-brunner, M.; Heib, C.; Horl, W. if Software-Entwicklung in der Chemie-Proceedings of the 9th Workshop, Bitterfeld, 16.-18.11.1994 (Ed.: R. Moll), Gesellschaft Deutscher Chemiker, Frankfurt am Main, 1995, pp. 113-28. see also Balkenhohl, F.; Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C.*Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2288-2337.

15. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366-374.

16. Weber, L.; Wallbaum, S.; Broger, C.; Gubernator, K. *Angew. Chem. Int. Ed. Engl.,* **1995**, *34*, 2280-2282.

17. Armstrong, R.W.; Salvati, M.E.; Nguyen, M.; *J. Am. Chem. Soc*., **1992**, *114*, 3144.

18. a)Moran, E.J.; Tellow, J.E.; Zhao, Z.; Armstrong, R.W. *J. Org. Chem*. **1993**, *58*, 7848, b) Armstrong, R.W.; Tellew, J.E.; Moran, E.J.; *J. Org. Chem.* **1992**, *57*, 2208.

19. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem.Res*. **1996**, *29*, 123-131.

20. Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem*. **1997**, *62*, 2917-2924.

21. There are about 24 isocyanides available (see ref. 20).

22. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc*. **1995**, *117*, 7842-7843.

23. Rosendahl, F.K.; Ugi, I. *Ann. Chem.* **1966**, *666*, 65-67.

24. Keating, T.A.; Armstrong, R.W. *J. Am. Chem. Soc.,* **1996**, *118*, 2574-2583.

25. Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron*, **1999**, *55*, 7411-7420.

26. Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron*, **1999**, *55*, 8189-8198.

27. Paulvannan, K, Tetrahedron Lett., **1999**, *40*, 1851-1854.

28. Lee, D. S.; Sello, J. K.; Schreiber, S. L. *Org. Lett.,* **2000**, *2*, 709-712.

29. Wright, D.L.; Robotham, C.V. Unpublished Results 2000.

30. Norman, B. H.; Shih, C.; Toth, J. E.; Ray, J. E.; Dodge, J. A.; Johnson, D. W.; Rutherford, P. G.; Schultz, R. M.; Worzalla, J. F.; Vlahos, C. J. *J. Med. Chem*. **1996**, *39*, 1106-1111.

31. Brian, P.W.; Curtis, P.J.; Hemming, H.G.; Norris, G.L.F. *Trans. Brit. Mycol. Soc.* **1957**, *40*, 366.

32. Powis, G; Bonjouklian, R.; Berggren, M.M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W.F.; Dodge, J.; Grindey, G.; Vlahos, C.J. *Cancer Res.* **1994**, *54*, 2419-2423.

33. Walker, E.; Pacold, M.E.; Perisic, O.; Stephans, L.; Hawkins, P.T.; Wymann, M.; Williams, R.L. *Molecular Cell*, **2000**, *6*, 909-919.

34. Powis, G. *Trends Pharm. Sci.* **1991**, *12* (5), 188-194.

35. Rodriguez-Viciana, P.; Warne, P. H.; Dhand, R.; Vanhaesebroeck, B.; Gout, I.; Fry, M. J.; Waterfield, M. D.; Downward, J. *Nature* **1994**, *370*, 527-532

36. Hawkins PT, Welch H., McGregor A, Eguinoa A., Gobert S., Krugmann S., Anderson K., Stokoe D., Stephens L *Biochem. Soc. Trans*. **1997**, *25*, 1147-1151.

37. Abbas, H. K.; Mirocha, C. J. *Appl. Environ. Microbiol*. **1988**, *54*, 1268-1274.

38. Schultz, R. M.; Andis, S. L.; Bonjouklian, R.; Merriman, R. L.; Powis, G.; Rutherford, P. G. *Proc. Am. Assoc. Cancer Res.* **1995**, 36, 316.

39. Powis, G; Bonjouklian, R.; Berggren, M.M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W.F.; Dodge, J.; Grindey, G.; Vlahos, C.J. *Cancer Res.* **1994**, *54*, 2419-2423.

40. Norman, B. H.; Shih, C.; Toth, J. E.; Ray, J. E.; Dodge, J. A.; Johnson, D. W.; Rutherford, P. G.; Schultz, R. M.; Worzalla, J. F.; Vlahos, C. J. *Journal of Medicinal Chemistry* **1996**, *39*, 1106-1111.

41. Powis, G; Bonjouklian, R.; Berggren, M.M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W.F.; Dodge, J.; Grindey, G.; Vlahos, C.J. *Cancer Res.* **1994**, *54*, 2419-2423.

42. Broka, C.A.; Ruhland, B. *J. Org. Chem.* **1992**, *57*, 4888-4894.

43. Sato, S.; Nakada, M.; Shibasaki, M. *Tetrahedron. Lett.* **1996**, *37*, 6141-6144.

44. Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron. Lett.* **1999**, *40*, 311-314.

45. (a) Ugi, I.; Domling, A.; Horl, W. *Endeavour* **1994**, *3,* 115. (b) Ugi, I., Goebel, M.; Gruber, B.; Heilingbrunner, M.; Heib, C.; Kern, O.; Starnecker, M. Res. Chem. Intermed. **1996**, 7, 625.

46. (a) Paulvannan, K.; Jacobs, J.W. *Tetrahedron* **1999**, *55*, 7433 (b) Paulvannan, K. *Tetrahedron Letters* **1999**, *40*, 1851.

47. Lee, D.; Sello, J.K.; Schreiber, S.L.; *Org. Lett.*, **2000**, *5*, 709.

48. Keay, B.A.; Rauk, A.; Hunt, I.R. *J. Org. Chem*. **1996**, *61*, 751.

49. Maggiani, A.; Tubul, A.; Brun, P. *Chem. Commun*. **1999**, *24*, 2495.

50. For examples see: (a) Rishton, G. M., Retz, D.M, Tempest, P.M., Novotny, J., Kahn, J., Treanor, J.S., Lile, J.D. and Citron, M. *J. Med. Chem.,* **2000** , *43*,2297-2299. (b) Karan, C. and Miller, B.L *Drug Design Trends*, **2000**, *5*, 67-75. (c) Frutos, O. and Curran, D. *J. Comb. Chem.,* **2000**, *2*, 639-649.

51. For examples see: (a) Uozumi, Y., Mizutani, K. and Nagai, S. *Tetrahedron Letter*, **2000**, *42*, 407-410. (b) Miller, S.J. and Copeland, G.T. *J. Am. Chem. Soc.*, **1999**, *121*, 4306-4307.

52. For an example see: Gilbertson, S.R., Chen, G., Kao, J., Beatty, A. and Campana, C.F *J. Org. Chem.*, **1997**, *62*, 5557-5566.

53. Xiang, X-D., Schultz, P.G. *Current Opinion in Solid State & Materials Science*, **1998**, *3,* 153-158.

54. Basso, A., Banfi, L., Riva, R., Piaggio, P. and Guanti, G. *Tetrahedron Letters*, **2003**, *44*, 2367-2370.

55. de Nooy, A. E. J., Masci, G. and Crescenzi, V. *Macromolecules*, **1999**, *32,* 1318-1320.

56. Presented in part at The Second International Conference on Multicomponent Reactions, Combinatorial and Related Chemistry, Genoa, Italy, April 14-16, 2003.

57. Heck, S. and Ugi, I. *Combinatorial Chemistry & High Throughput Screening*, **2001**, *4*, 1-34.

58. Ugi, I., Domling, A. and Horl, W. *Endeavour*, **1994**, *3*, 115.

59. Trost, B.M. and Hachiya, I. *J. Am. Chem. Soc.*, **1998**, *120*, 1104-1105.

60. (a) Murara, H.; Sanda, F. and Endo, T. *Macromolecules*, **1996,** *29*, 5535-5538. (b) Langer, R. *Acc. Chem. Res.*, **2000**, *33*, 94-109.

61. For reviews on catalytic olefin metathesis, see: a) Grubbs, R.H., Miller, S.J., Fu, G.C. *Acc. Chem. Res.,* **1995**, *28*, 446-452. b) Schmalz, H, -G., *Angew. Chem., Int. Ed.*, **1995**, *34*, 1833-1836. c) Schuster, M. and Blechert, S., *Angew. Chem., Int. Ed.*, **1997**, *36*, 2036-2056. d) Wright, D.L., *Curr. Org. Chem.*, **1999**, *3*, 211-240.

62. (a) Liaw,D,-J, Tsai, J,-S and Wu, P,-L. *Macromolecules*, **2000**, *33*, 6925-6929. (b) Nomura, K. and Schrock, R.R. *Macromolecules*,**1996**, *29*, 540-545. (c) Maynard, H.D., Okada, S. and Grubbs, R.H. *Macromolecules*, **2000**, *33*, 6239-6248. (d) Roberts, K.S. and Sampson, N.S. *J. Org. Chem.*,**2003**, *68,* 2020-2023.

63. I. Ugi, U. Fetzer, U. Eholzer, H. and Knupfer, K. *Angew. Chem.*, **1965**, 77, 492-504; *Angew. Chem. Int. Ed. Engl.*,**1965**, *4*, 452-464.

64. Trnka, T.M. and Grubbs, R.H. *Acc. Chem. Res.*, **2000**, *34*, 18-29.

65. Bielawski, C.W. and Grubbs, R.H. *Angew. Chem. Int., Ed.*,**2000**, *39*, 2903-2906.

66. Corey, E.J., Shibata, T. and Lee, T.W. *J. Am. Chem. Soc.*, **2003**, *124*, 3808-3809.

67. Frigerio, M.; Santagostino, M.; Sputore, S.J. *J. Org. Chem.* **1999**, *64*, 4537.

68. Singh, V.K.; Chen, C.P., Shibata, S.; Bakshi, R.K.; Corey, E.J. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

69. Drian, C.L.; Signorella, S.; Chaumeil, H. *Tetrahedron*. **2000**, *56*, 9655.

70. Stork, G. and Sher, P.M. *J. Am. Chem. Soc.* **1986**, *108,* 303-304.

71. Luche, J.L. *J. Am. Chem. Soc.* **1978**, 100, *7*, 2226.

72. Mitsunobu, O. *Synthesis*. **1981**, 1.

73. Segmuller, B.E.; Etheredge, S.J.; Ciufolini, M.; Berman, E.M.; Danishefsky, S. *J. Am. Chem. Soc.* **1985**, 107, 3891.

74. Alvi, K.A.; Rodriguez, J.; Diaz, M.C.; Moretti, R.; Wilhelm, R.S.; Lee, R.H.; Slate, D.L.; Crews, P. *J. Org. Chem.* **1993**, *58*, 4871.

BIOGRAPHICAL SKETCH

Claude V. Robotham was born in Queens, New York, in 1972. He received his B.S. in chemistry from Hofstra University in 1996 and a M.S. in physical chemistry in 1998 from Illinois State University under the direction of Dr. Cheryl Stevenson where he investigated the chemistry of free radicals. Since 1998 he has worked with Prof. D.L. Wright at the University of Florida on the chemistry and biology of viridin natural products and new methods in multi-component coupling reactions.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Dennis L. Wright, Chairman
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Gus J. Palenik
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth B. Sloan
Professor of Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 2003

Dean, Graduate School